CHEMICAL INVESTIGATIONS IN ALICYCLIC SYSTEMS WITH SPECIAL REFERENCE TO STEROIDS

DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE AWARD OF THE DEGREE OF

Master of Philosophy

IN

Chemistry

DILSHAD AHMAD

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH [INDIA]

1989

Aligarh Muslim University
Aligarh - 202 002

Dr. M. Mushfiq
Reader
Department of Chemistry

Date : 25.4.89

This is to certify that the dissertation entitled 'Chemical Investigation in Alicyclic Systems with special Reference to Steroids' by Mr. Dilshad Ahmad is suitable for submission for the award of the degree of Master of Philosophy in Chemistry.

(Dr. M. Mushfiq)

ACKNOWLEDGEMENT

My deep sense of gratitude is due to Dr. M. Mushfiq for his able guidance, encouragement and keen supervision throughout the work from the beginning. I am highly indebted to Prof. M.S. Ahmad former chairman, Deptt. of Chemistry for his guidance. I am also beholden to Prof. S.M. Osman, Chairman Deptt. of Chemistry for providing necessary facilities.

I deem it my most pleasant duty to acknowledge my indebtedness and convey my thanks to my seniors for their invaluable counsel.

I am thankful to my research colleagues for their kind cooperation in giving the final shape to this dissertation. The painstaking job of typing by Mr. Mohd. Ayub is highly appreciated.

Dilshad Ahmad

(Dilshad Ahmad)

C O N T E N T S

INTRODUCTION

After the discovery of cholesterol, the study of steroidal compounds has become most interesting and thoroughly explored area for organic chemists. First steroid compound was extracted by Cherveul in 1812. After that, the discovery of sex hormones such as aldosterone, Oestrogen expanded the interest of steroidal compounds. The physiological activities of steroidal hormones and their role in various metabolism, the discovery of several biologically active steroids, such as corticoids with their wide application in therapy and the preparation of modified steroids with interesting facets of chemistry, all afforded wealth of material of tremendous interest. The discovery of naturally occurring oxygen and nitrogen containing steroid endowed with pronounced biological and pharmacological activities, has drawn the attention of chemists towards the syntheses of hetero-steroids[1-4].

Some of the steroidal derivatives showed interaction with some enzyme systems as anti-hormones, for the same, azasteroid i.e., nitrogen containing steroids are recieving concerned attention of chemists and pharmacologists alike. Allauddin and Martin-Smith[5-6] and Surgue have reviewed biological activity in steroid possessing nitrogen atom, both of natural and synthetic origin.

The modification in the structure of steroids have shown biological activity of one kind or the other, some of them are of clinical significance and a few are entering in the field of medicinal practice with good potential acceptance as reliable drugs. There are known aza-steroids, oxa-steroids which have anabolic, anti-hormonal, anti-hypercholest, vasodialatory, anti-cancer, neuro-muscularblocking, CNS depressant or anti-microbial activity.

Our laboratory, concerned mainly with the synthesis of organic compounds and their identification and characterization by chemical and spectral studies, has been engaged for last two decades in the preparation of modified steroids. The synthesis of a large number of oxa and aza-steroids, mainly from cholestane and stigmastane series, has been reported. In the write up an attempt has been made to give a brief survey of the literature on the relevent reactions being used for various mocifications in the steroidal molecules mainly in the cholestane and stigmastane series. This also includes some of the preliminary studies made and the proposal for the future research programme.

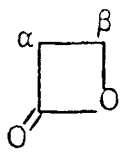
CHAPTER-ONE

Mn (III)ACETATE AS AN OXIDIZING AGENT

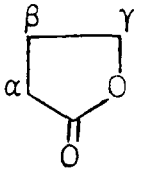
THEORETICAL

In this present work effect of Mn(III) acetate has been studied on steroidal unsaturated oximes, therefore, it is pertinent to mention the use of Mn(III) acetate as an oxidizing agent under different oxidative conditions.

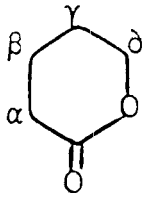
Olefins on oxidation with Mn(III) acetate result in the formation of γ-lactone[8]. The lactone ring which can be easily formed or broken shows wide variations with change of ring size and with the nature and degree of substitutions on ring carbon atoms. Generally γ-lactones are regarded as most stable, which on hydrolysis give γ or 4 hydroxy acids. Lactones are hetero-cyclic compounds, viz. 2-oxo-oxetan or β-butyrolactone (I), 2-oxo-oxolan or γ-butyrolactone (II) and 2-oxo-oxane, ∂-valero lactone (III), but they are more usually named after the parent acids. Greek letter prefix is used to denote ring size as that used for the position of the hydroxy group related to the carboxylic function in the hydroxy acids.



(I)



(II)



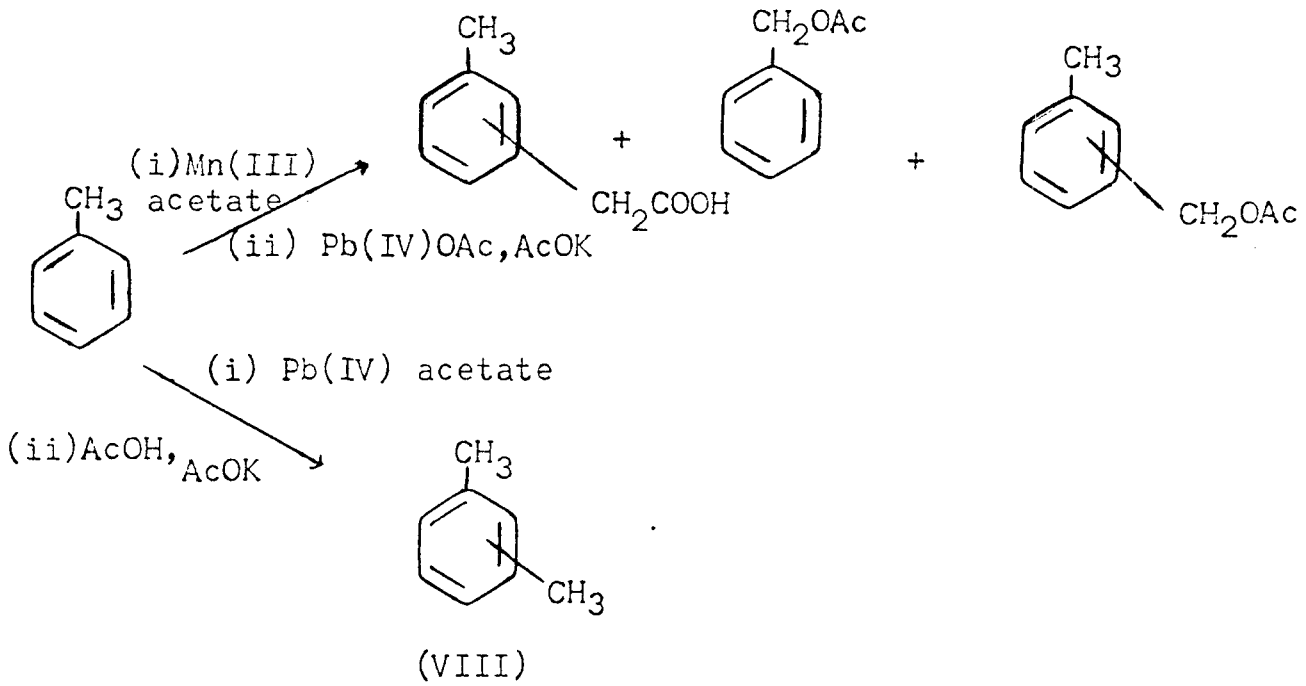
(III)

Many naturally occurring lactones show anti-bacterial properties, some of them are protoanemonin, penicillic acid, clavoic and crepin manifest antibiotic action by the possession of strong anti-bacterial properties against both gram +ve and grame -ve bacteria one of the important substances protoanemonin was first isolated from buttercup by Asahina and Fujita[9] and later from anemone pulsatilla by Baer et al.[10]

The discovery of biologically active lactones has stimulated interest in the synthesis of more lactones for which Mn(III) acetate has also been one of the reagents used successfully, this chapter gives a brief account of the use of Mn(III) acetate.

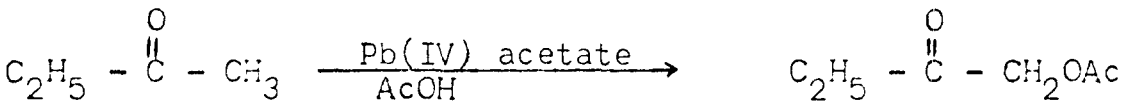
Mn(III) acetate acts as an oxidizing agent and most of the results have been successfully reported in terms of minor sphere one-electron transfer process[11]. The oxidation of organic compounds has also been studied which shows one-electron transfer process.

Toluene (IV) on oxidation by Mn(III) acetate in refluxing acetic acid or by Pb (IV) acetate in refluxing acetic acid containing potassium acetate under nitrogen atmosphere yielded three products[12], tolyl acetic acid (V), benzyl acetate (VI) and isomeric methyl benzyl acetate (VII). However, a minor amount of xylene (VIII) was also reported under the reaction conditions.

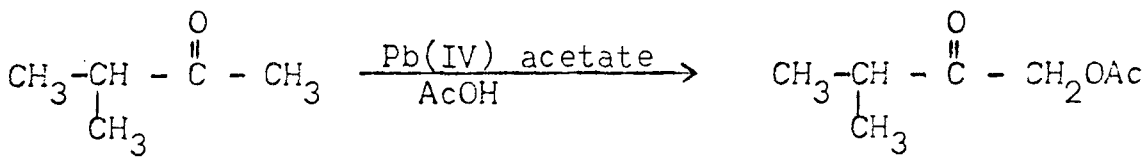


(VIII)

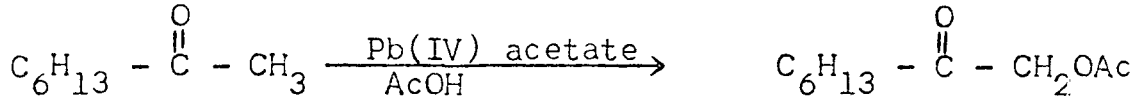
Moon et al.[13] showed that oxidation of 2-butanone (IX) 3-methyl-2-butanone (X) and 2-octanone (XI) with Pb(IV) acetate in acetic acid gave their respective oxidation products, 1-acetoxy-2-butanone (XII), 1-acetoxy-3-methyl-2-butanone (XIII) and 1-acetoxy-2-octanone (XIV)



(IX) (XII)



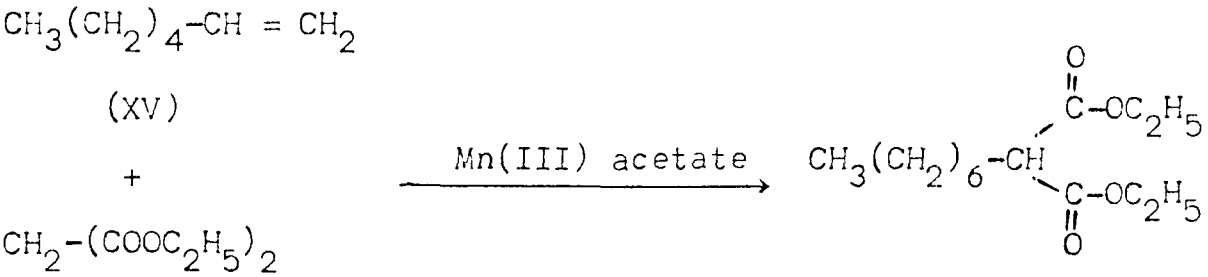
(X) (XIII)



(XI) (XIV)

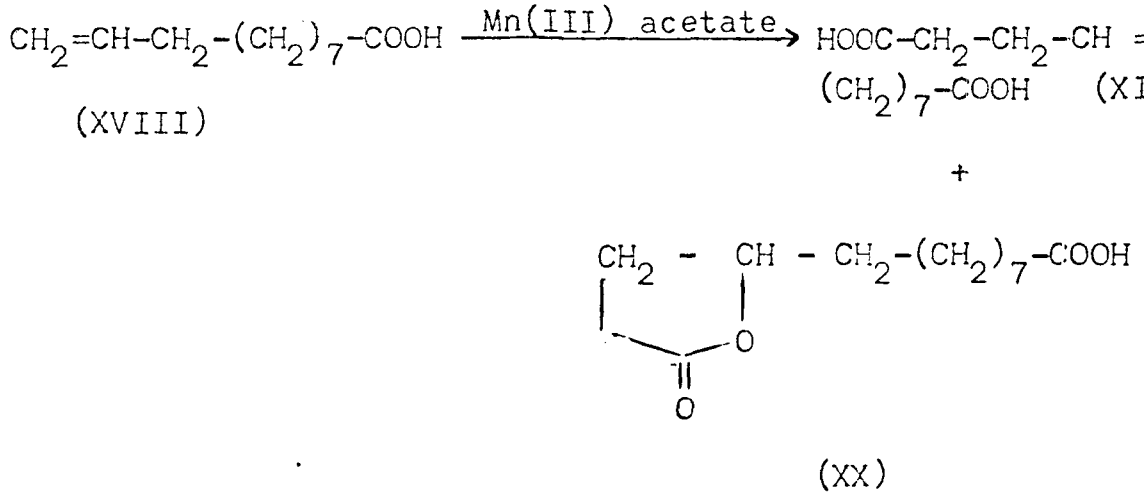
In the same way when the propionic acid was used the corresponding, propionoxy ketones were obtained along with acetoxy derivatives as minor products.

Nikishin et al.[14] carried out the treatment of hept-1-ene (XV) with diethyl malonate (XVI) in the presence of Mn(III) acetate at 90° and reported the formation of n-heptyl malonate (XVII) in 50% yield.



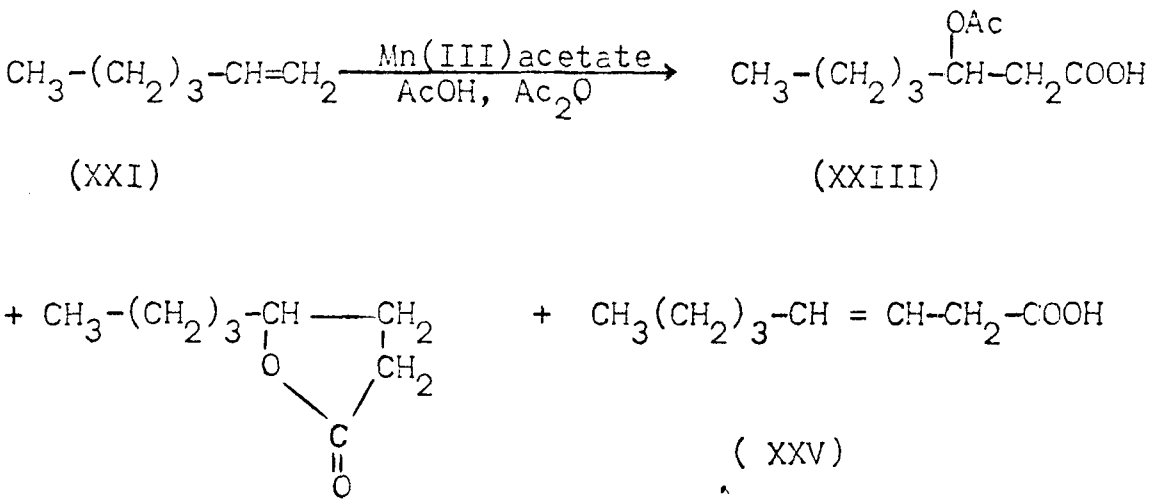
(XV) (XVI) (XVII)

Osman and coworkers[15] reported that formation of 10-decenoic acid (XVIII) with Mn(III) acetate afforded two products, 4-tridecene dioic acid (XIX) and 5-(ω-carboxy-octyl)-γ-butyrolactone (XX).

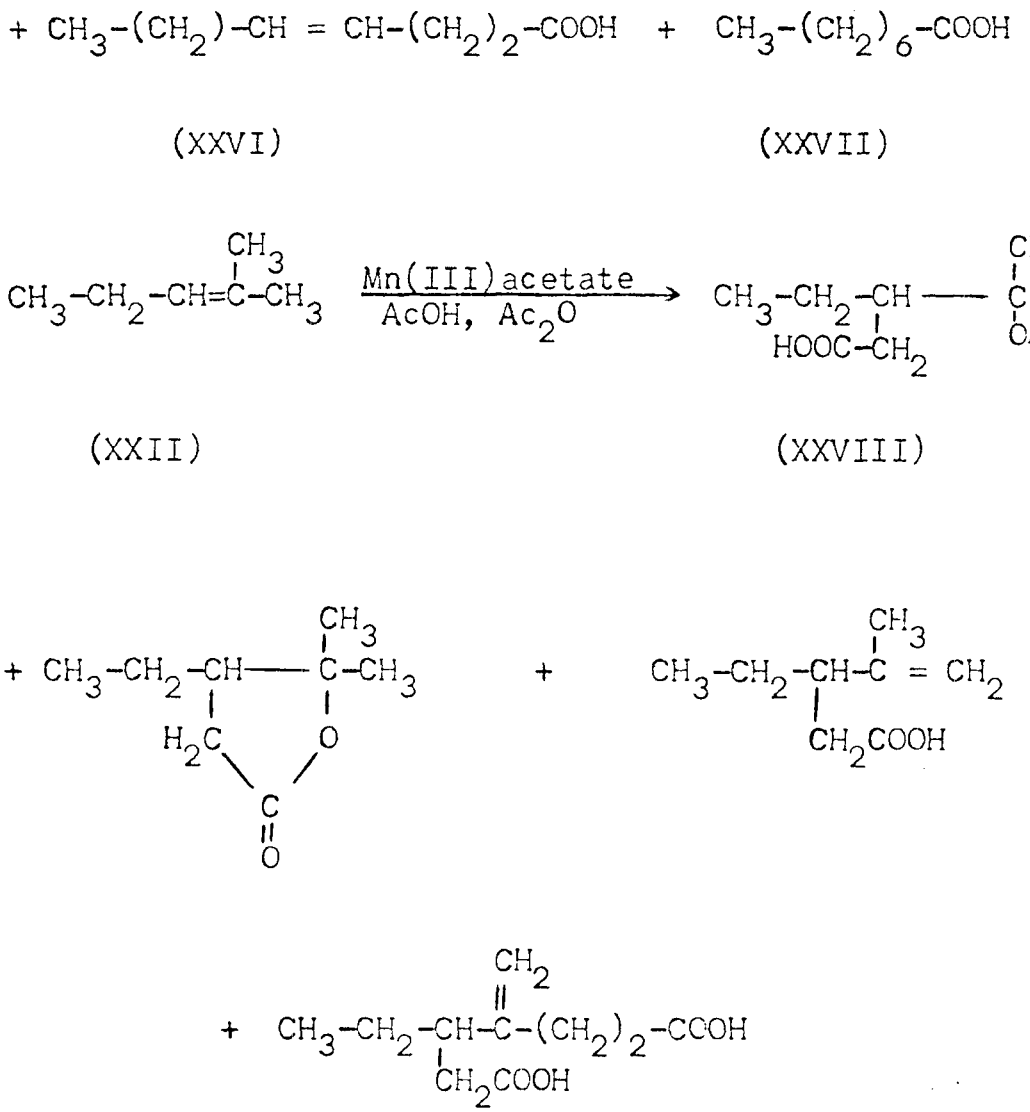


(XVIII) (XIX) (XX)

Okano and coworkers[16] reported the reaction of 1-hexene (XXI) and 2-methyl-2-pentene (XXII) with Mn(III) acetate in acetic acid and acetic anhydride. 1-Hexene (XXI) afforded 4-acetoxyoctanoic acid (XXIII), γ-lactone of 4-hydroxy octanoic acid (XXIV), 3-octenoic acid (XXV), 4-octenoic acid (XXVI) and octanoic acid (XXVII). The alkene (XXII) gave 4-acetoxy-3-ethyl-4-methylpentanoic acid (XXVIII), γ-lactone of 3-ethyl-4-hydroxy-4-methylpentanoic acid (XXIX), 3-isopropenyl pentanoic acid (XXX) and 3-ethyl-4-methylene-heptanedioic acid (XXXI).



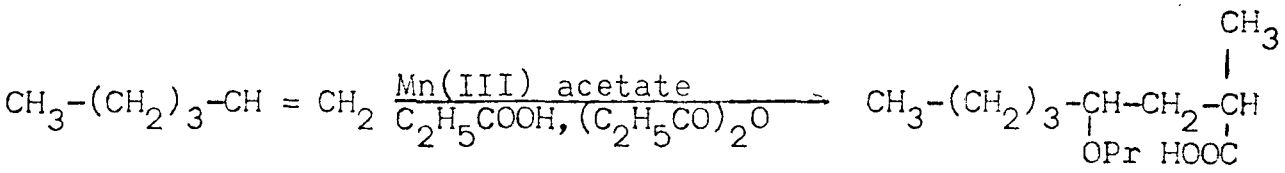
(XXI) (XXIII) (XXIV) (XXV)



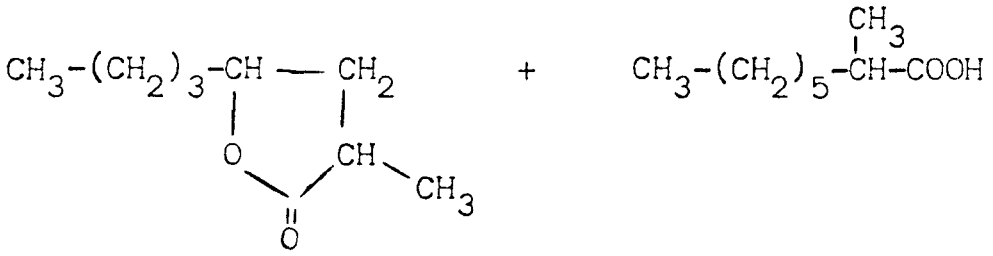
(XXVI) (XXVII)

(XXII) (XXVIII)

However, the oxidation of 1-hexene (XXI) with Mn(III) acetate in propionic acid and propionic anhydride afforded 2-methyl-4-propionyloxyoctanoic acid (XXXII), γ-lactone of 4-hydroxy-2-methyloctanoic acid (XXXIII) and 2-methyloctanoic acid (XXXIV), whereas (XXII)[16] under similar reaction conditions afforded γ-lactone of 2,4-dimethyl-3-ethyl-4-hydroxypentanoic acid (XXXV), 3-ethyl-2,4-dimethyl-4-pentenoic acid (XXXVI) and 3-ethyl-2,6-dimethyl-4-propionyloxymethyl-1,7-heptanedioic acid, (XXXVII).

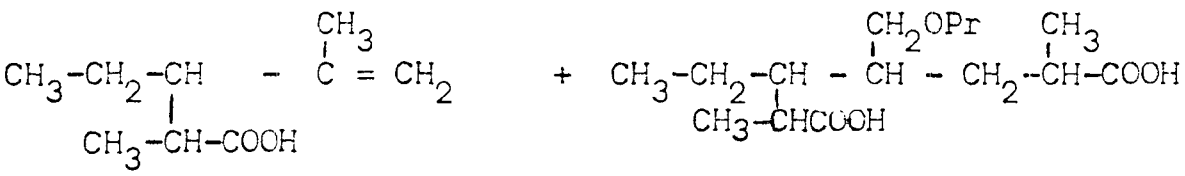


(XXI) (XXXII)



(XXXIII) (XXXIV)

(XXII) (XXXV)

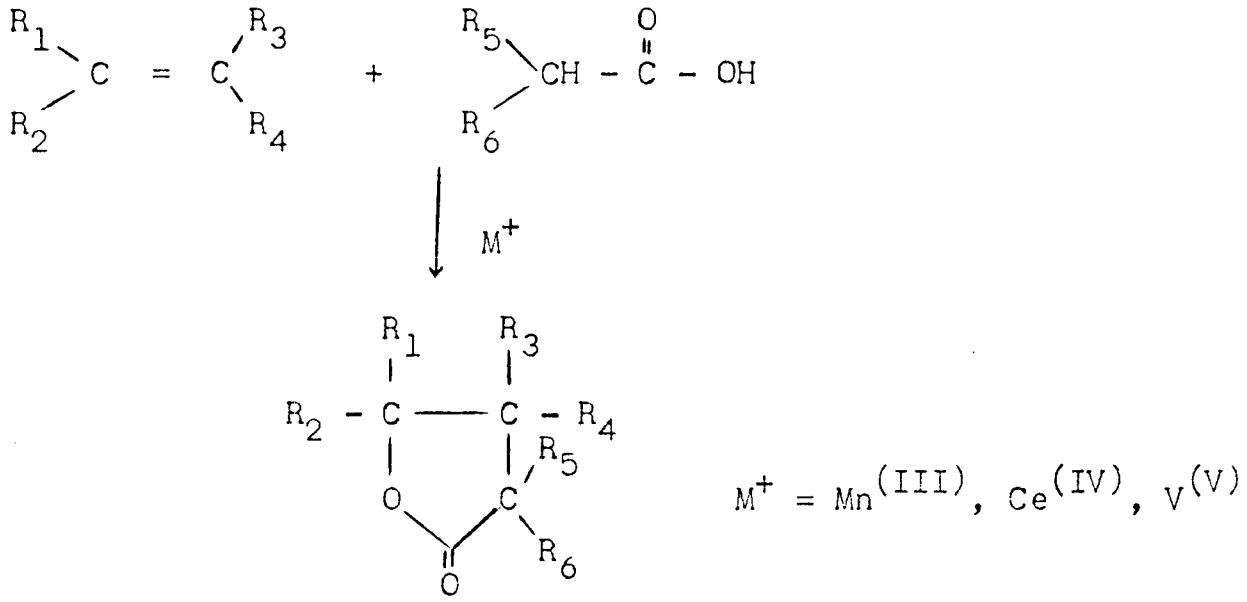


(XXXVI) (XXXVII)

When the reaction of 1-methyl cyclohexene with Mn(III) acetate was carried out in acetic acid with radioactive carbon,

γ-Lactone[17-18] acetate obtained showed the presence of lebelled carbon. This indicates that solvent participates in the reaction of alkenes with Mn(III) acetate. On heating Mn(III) acetate (dihydrate) at 100°C, an appreciable amount of succinic acid and a trace of acetoxy acetic acid were isolated. These results demonstrated the formation of radicals $\dot{C}H_2COO$, $CH_3COO^{\bullet}$, $CH_3-\dot{C}H-COOH$ and $CH_3CH_2COO^{\bullet}$ with the participation of solvent in the Mn(III) acetate reaction.

Heiba et al.[19] synthesized γ-butyrolactones with olefins and carboxylic acid in a simple one-step process.



$M^+ = Mn^{(III)}, Ce^{(IV)}, V^{(V)}$

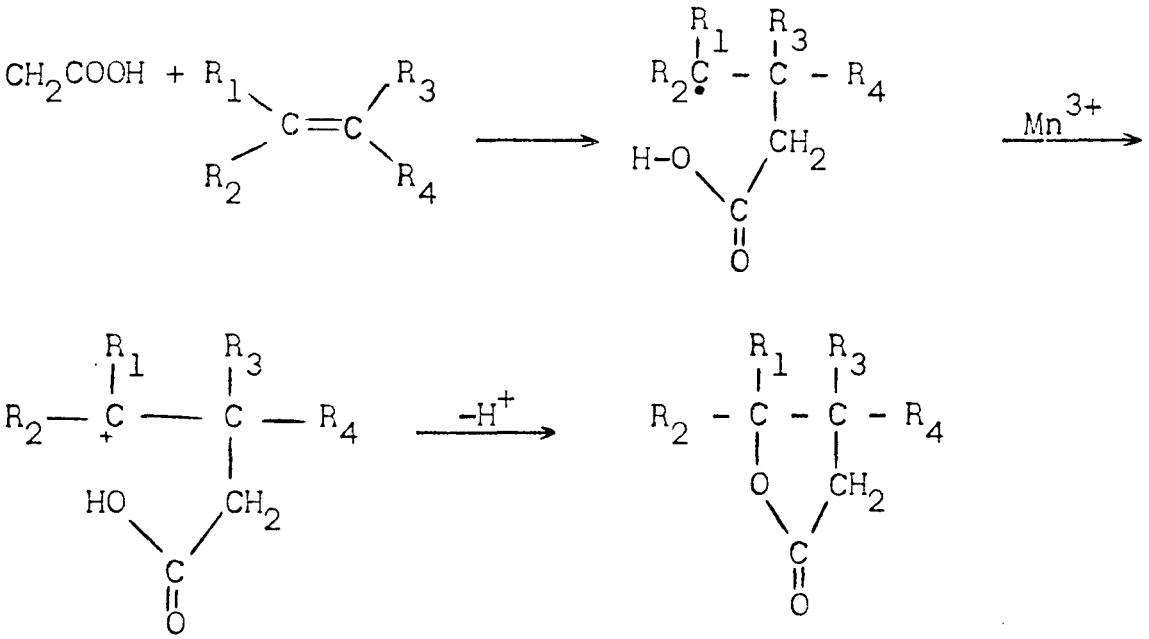
Higher valent metal salts of manganese, Cerium and vanadium have been used successfully in the lactone synthesis. The manganese reagent used was the acetate dihydrate $Mn(OAc)_3.2H_2O$

which was readily prepared by permanganate oxidation of manganous acetate and could be stored for extended period of time. Generally this reaction is conducted at the temperature range 120 - 180^{o} in a refluxing system.

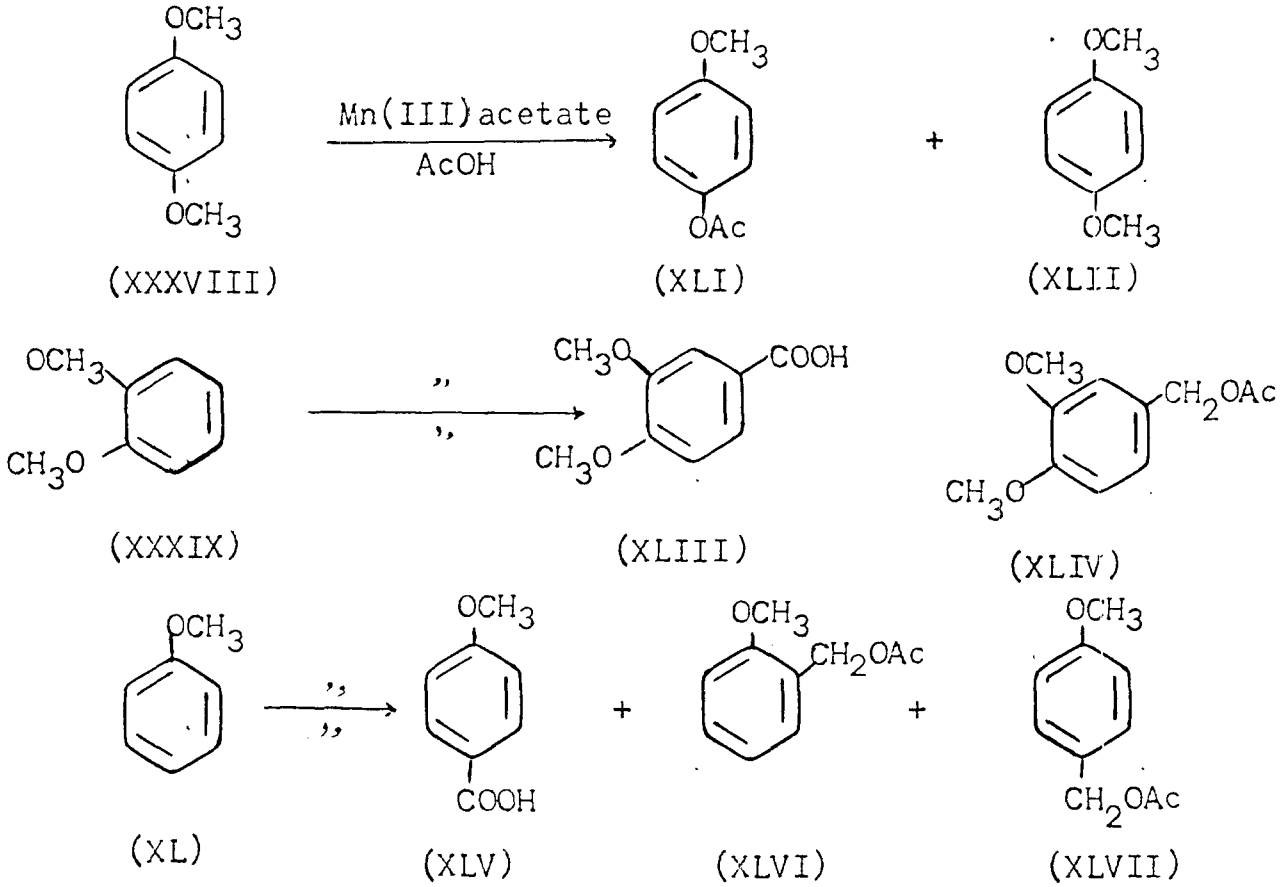
In the lactone synthesis it was found advantageous to add 10 - 30% potassium acetate to the reaction mixture, this addition of acetate ion shortened the reaction time by raising the reflux temperature of the reaction mixture and decrease the formation of side products. This effect of suppresing side reaction was especially important, when high concentration of conjugated olefins, such as styrene, was used.

Free carboxy methyl radical as an intermediate has been demonstrated by thermal decomposition of manganic acetate. According to this, the following mechanism has been proposed for the lactone synthesis (Scheme-1)[19].

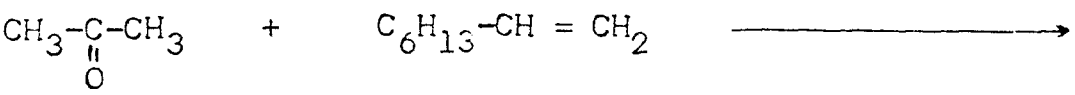
Scheme - 1



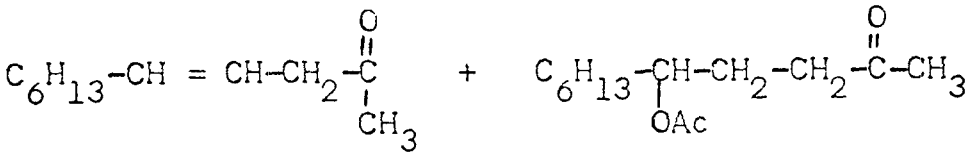
Aratani et al.[20] reported that hydroxyquinone dimethyl ether (XXXVIII), veratole (XXXIX) and anisole (XL), on reaction with Mn(III)acetate in refluxing acetic acid afforded their respective oxidation products (XLI and XLII), (XLIII and XLIV), (XLV - XLVII).



Reaction of acetone (XLVIII) with 1-octene (XLIX)[21] in the presence of Mn(III)acetate under nitrogen atmosphere using acetic acid as a solvent afforded the unsaturated ketone (L), and keto acetate (LI).

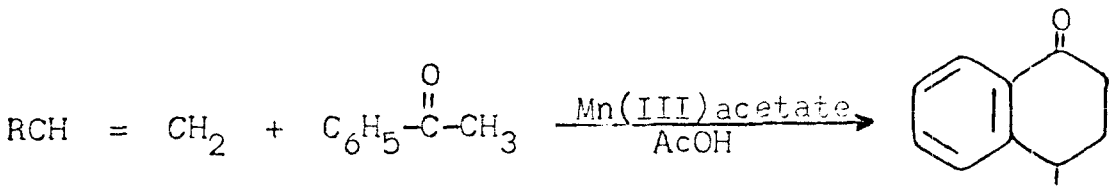


(XLVIII) (XLIX)



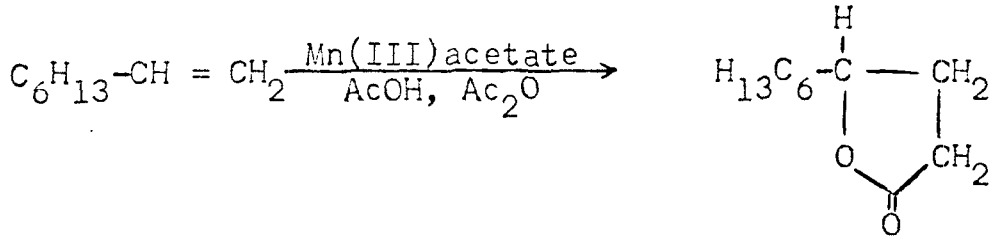
(L) (LI)

Similarly oxidation of olefins (LII) with acetophenone (LIII)[22] in the presence of Mn(III)acetate and acetic acid provided α-tetralone (LIV) in about 50% yield.

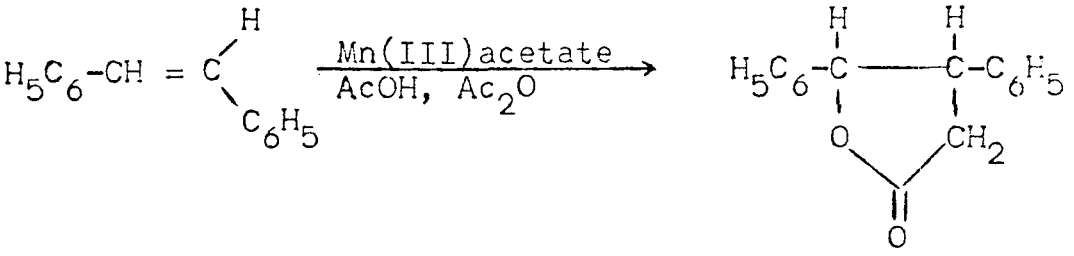


(LII) (LIII) (LIV)

Heiba et al.[23] carried out the oxidation of 1-octene (XLIX) and trans-stilbene (LV) in the presence of acetic anhydride and obtained their corresponding γ-lactones (LVI), (LVII).

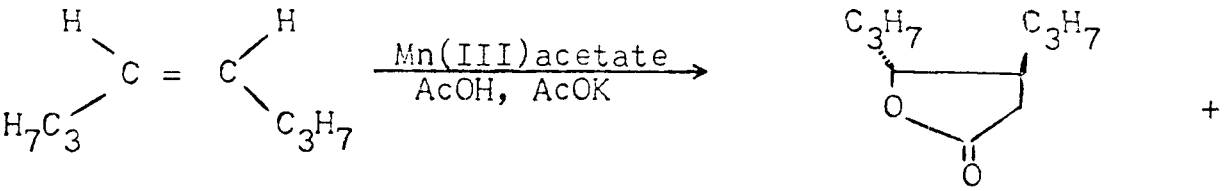


(XLIX) (LVI)

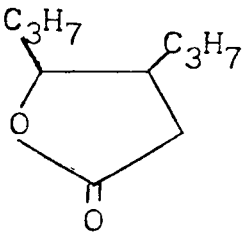


(LV) (LVII)

Recently, Fristad and Peterson[24] reported the oxidation of a number of olefins, such as cis-octene-4 (LVIII), trans-octene-4 (LIX), cyclo hexene (LX), cycloheptene (XLI) and cyclooctene (LXII) with Mn(III)acetate in acetic acid and potassium acetate. These afforded their corresponding isomeric γ-lactones, trans-dihydro-4,5-dipropyl-2 (3H) furanone (LXIII), cis-dihydro-4,5-dipropyl-2(3H)-furanone (LXIV), trans-hexahydro-2 (3H)-benzofuranone (LXV), cis-hexahydro-2 (3H)-benzofuranone (LXVI), trans-octahydro-2H-cyclohepta [b] furan-2-one (LXVII), cis-octahydro-2H-cyclohepta [b] furan-2-one (LXVIII), trans-octahydrocycloocta [b] furan-2(3H)-one (LXIX) and cis-octahydro-cycloocta [b] furan-2(3H) one (LXX).

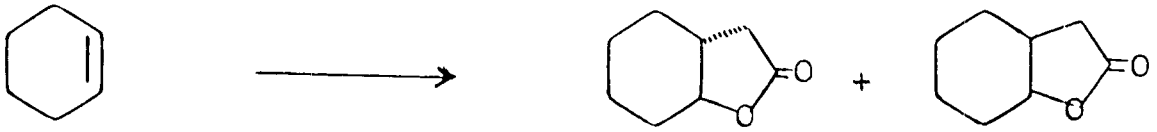


(LVIII) (LXIII)

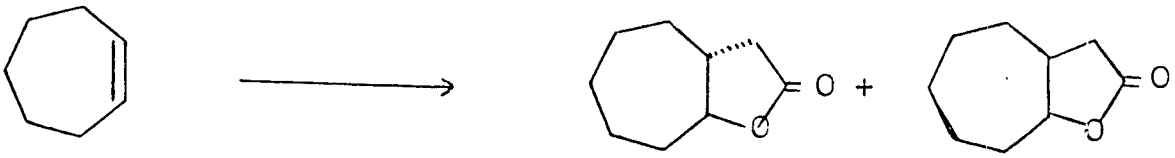


(LXIV)

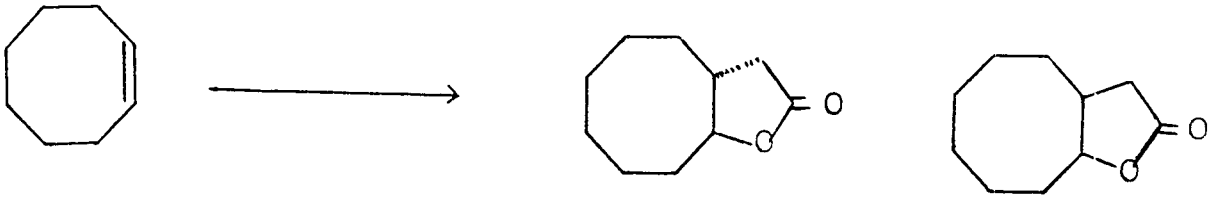
(LXIII) + (LXIV)



(LX) (LXV) (LXVI)

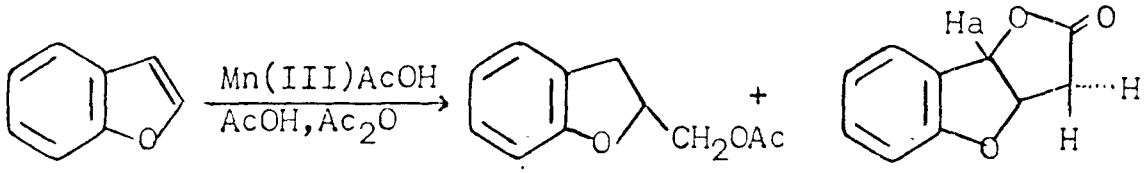


(LXI) (LXVII) (LXVIII)

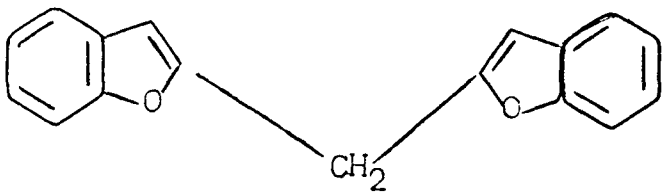


(LXII) (LXIX) (LXX)

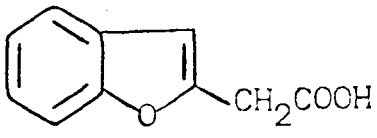
Kasahara and coworkers[25] reported that oxidation of benzofuran (LXXI) with Mn(III)acetate in presence of acetic acid and acetic anhydride yielded four products, namely 2-(acetoxy methyl) benzofuran (LXXII), 3a,8b-dihydrofuro [3,2b] benzofuran-2(3H)-one (LXXIII) as the major products and bis(2-benzo furanyl) methane (LXXIV) and 2-benzofuranyl acetic acid (LXXV) as the minor products.



(LXXI) (LXXII) (LXXIII)

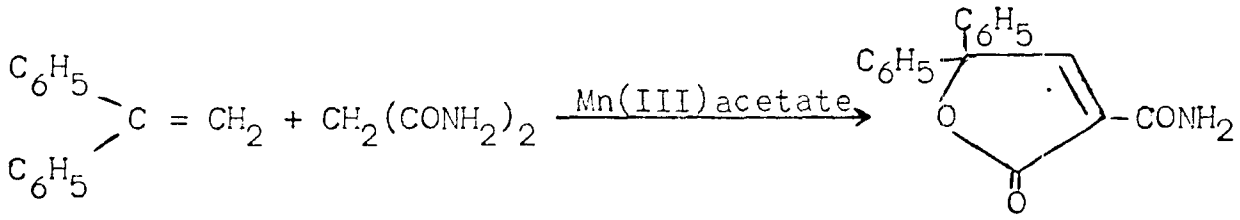


(LXXIV)

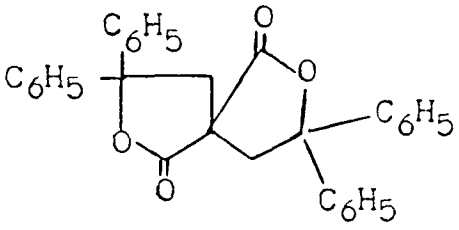


(LXXV)

Nishino and coworkers[26] reported the oxidation of 1, 1-diphenylethene (LXXVI) with malonamide (LXXVII) in the presence of Mn(III) and obtained 2-carbamoyl-4, 4-diphenyl-2-buten-4-olide (LXXVIII), 3,3,8,8-tetraphenyl-2,7-dioxaspiro [4,4] nonane-1, 6-dione (LXXIX) and benzophenone (LXXX).



(LXXVI) (LXXVII) (LXXVIII)



(LXXIX)

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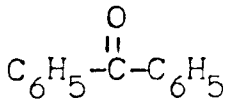
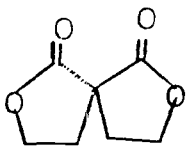
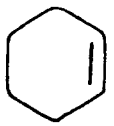
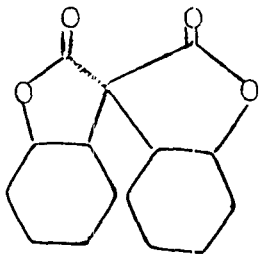


(LXXX)

Fristad et al.[27] reported the oxidation of ethylene (LXXXI) and cyclohexene(LX) with Mn(III)acetate in the presence of malonic acid using acetic acid as a solvent, they got spirotype products, such as 2,7-dioxaspiro [4,4] nonane-1, 6-dione (LXXXIII) and dodecahydro-3,3'-(2H,2H')-spirobi (benzofuran)-2', 2'-dione (LXXXIV).

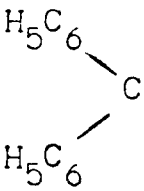
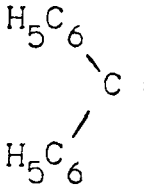
$CH_2 = CH_2 + CH_2(COOH)_2 \xrightarrow[AcOH]{Mn(III)acetate}$  (LXXXIII)

(LXXXI) (LXXXII)

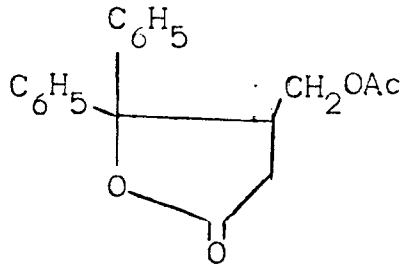
 + $CH_2(COOH)_2 \xrightarrow[AcOH]{Mn(III)acetate}$ 

(LX) (LXXXII) (LXXXIV)

Kurosawa and coworkers[28] reported that oxidation of 3,3-diphenyl-2-propenoic acid (LXXXV) with Mn(III)acetate in boiling acetic acid gave 3,3-diphenyl-2-propenyl acetate (LXXXVI), 4-acetoxymethyl-5,5-diphenyl tetrahydro-2-furanone (LXXXVII), 3,3-diphenyl-1-propenal (LXXXVIII), 5,5-diphenyl-2,5-dihydro-2-furanone (LXXXIX), 4-acetoxy-5,5-diphenyl tetrahydro-2-furanone (XC) and 2-oxo-5,5-diphenyl tetrahydro-4-furan carboxylic acid (XCI).

 = CH-COOH $\xrightarrow[AcOH,\ Ac_2O]{Mn(III)acetate}$  = $CH-CH_2-OAc$ +

(LXXXV) (LXXXVI)



(LXXXVII)

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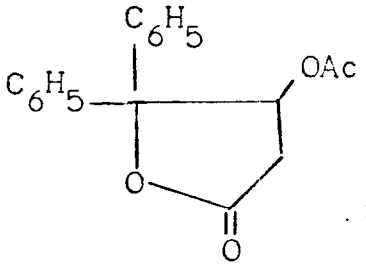
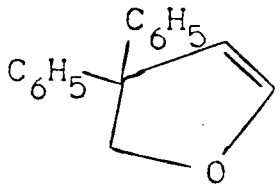
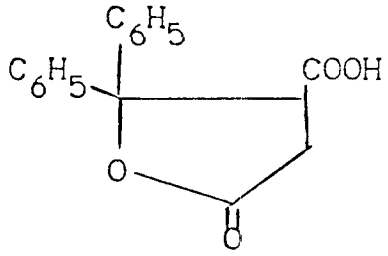


(XC)



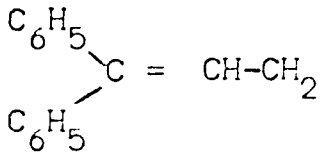
(LXXXIX)

+



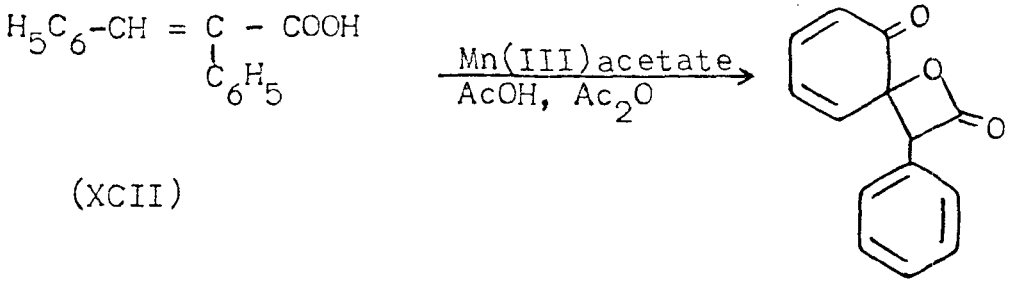
(XCI)

+



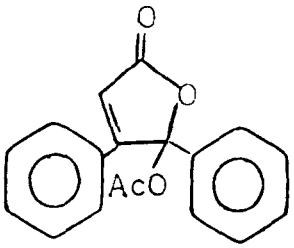
(LXXXVIII)

Kurosawa et al.[29] carried out the oxidation of α-phenyl cinnamic acid (XCII) with Mn(III)acetate in presence of acetic acid and acetic anhydride and obtained the spiro-lactone (XCIII) and 5-acetoxy-4,5-diphenyl-2 (5H)-furanone (XCIV).



(XCII)

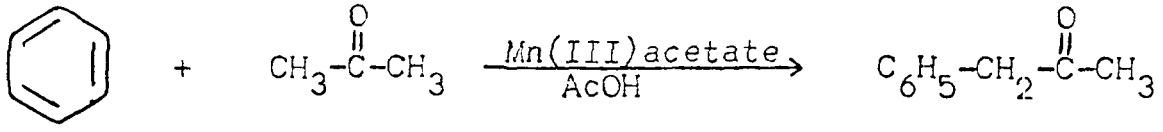
(XCIII)



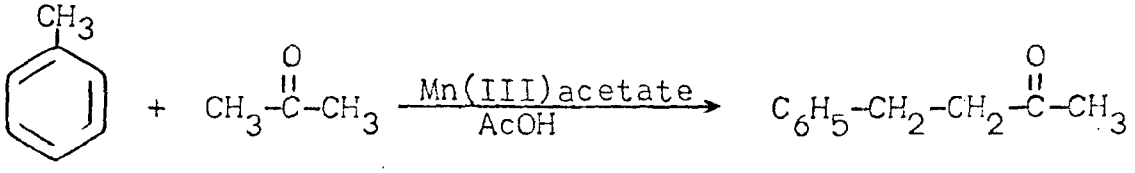
(XCIV)

Okano and coworkers[30] reported acetoxy ketones from simple ketones in presence of Mn(III)acetate and acetic-anhydride.

Kurz and coworkers[31] carried out the work on benzene (XCV) and toluene (IV) in the presence of acetone (XLVIII) with Mn(III)acetate using acetic acid, acitic anhydride as a solvent and reported the formation of (XCVI) & (XCVII), respectively.

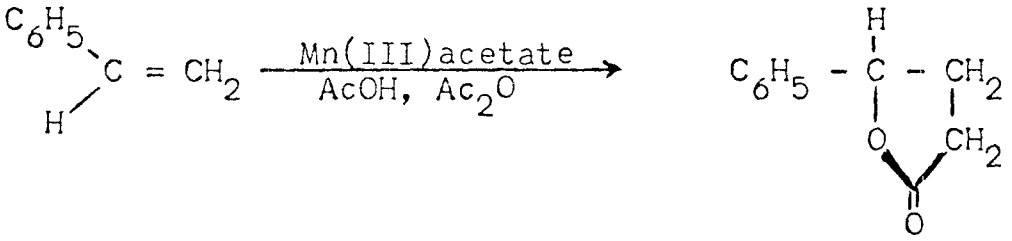


(XCV) (XLVIII) (XCVII)

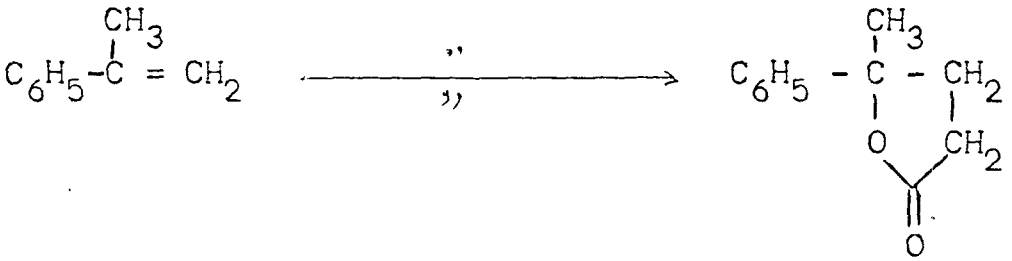


(IV) (XLVIII) (XCVII)

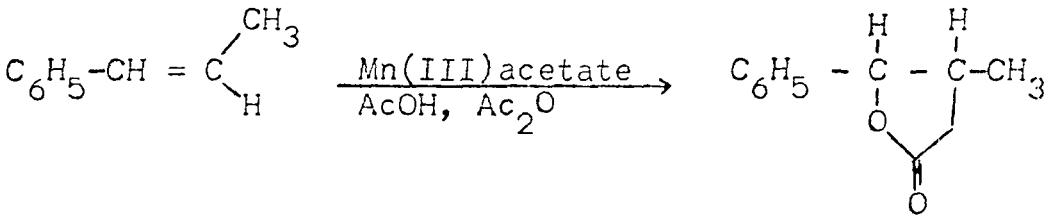
Bush and coworkers[32] reported the oxidation of styrene (XCVIII), α-methyl styrene (XCIX), β-methyl styrene (C) and 3,3-dimethyl-1-butene (CI) with Mn(III)acetate in acetic acid and acetic anhydride afforded their corresponding γ-lactones, 5-phenyltetrahydro-2-furanone (CII), 5-methyl-5-phenyl tetrahydro-2-furanone (CIII), 4-methyl-5-phenyl tetrahydro-2-furanone (CIV) and 5-tertiary butyl tetrahydro-2-furanone (CV).



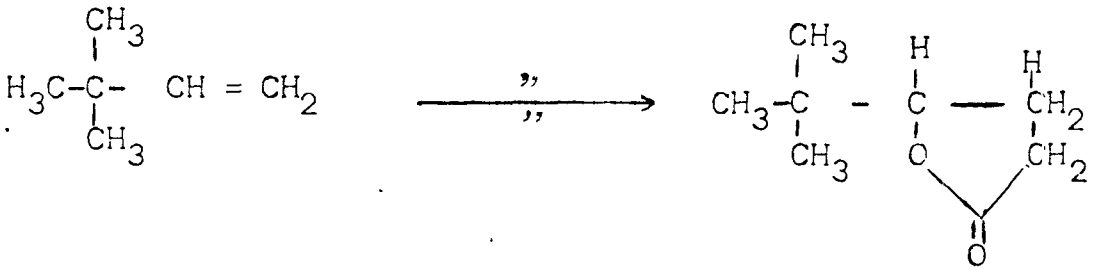
(XCVIII) (CII)



(XCIX) (CIII)

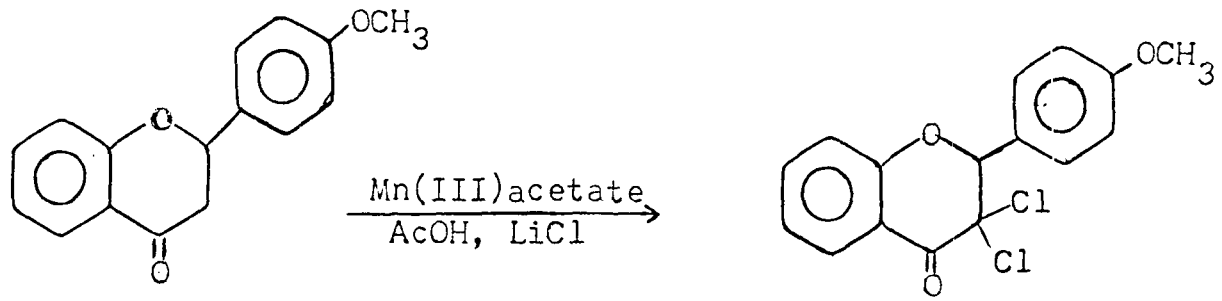


(C) (CIV)

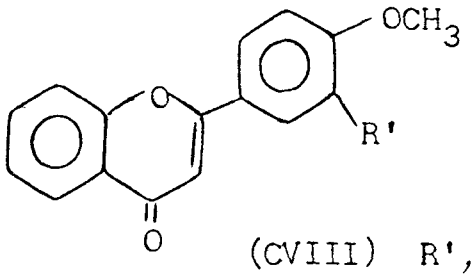


(CI) (CV)

Kurosawa and coworkers[33] reported that when 2-(4-methoxy-phenyl)-4-chromanone (CVI) was refluxed with Mn(III) acetate and acetic acid in the presence of HCl, the products were found to be 3,3-dichloro-2-(4-methoxyphenyl)-4-chromanone (CVII), 3-chloro-4-methoxy flavone (CVIII), and 4'-methoxy flavone (CIX).



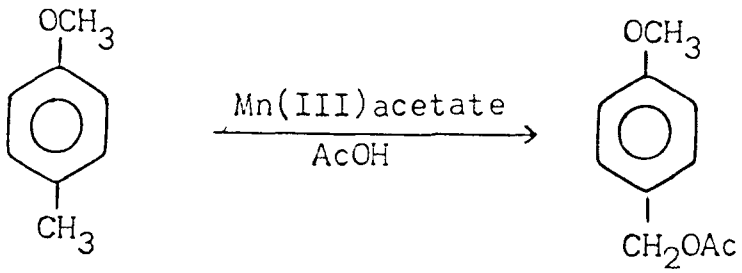
(CVI) (CVII)



(CVIII) R', Cl

(CIX) R', H

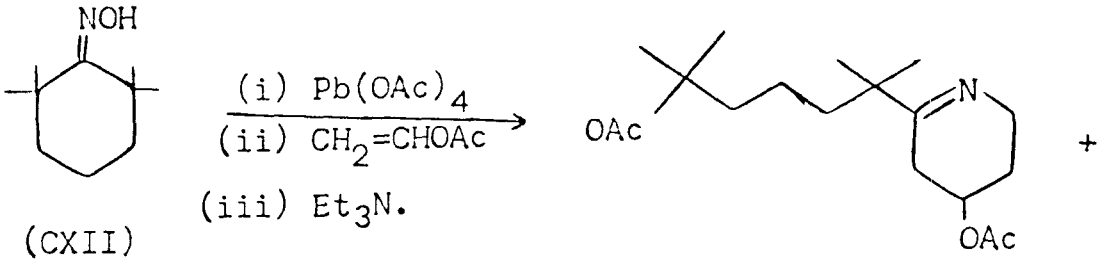
Andrulis, Jr. and coworkers[34] reported that treatment of p-methoxy toluene (CX) by Mn(III)acetate in acetic acid afforded p-methoxybenzyl acetate (anisylacetate) (CXI) as the only product.



There are two types of manganese (III) acetate, anhydrous[35] form and the other hydrated[36] one. It is stated that the hydrate form was much more efficient at lactone annulation, and was also shown that the addition of acetic anhydride decreases the yield of lactone[24]. In contrast, other workers have found that reaction containing acetic anhydride produced a mixture of products[16,17,37]. Previous reports have[32,38] indicated that

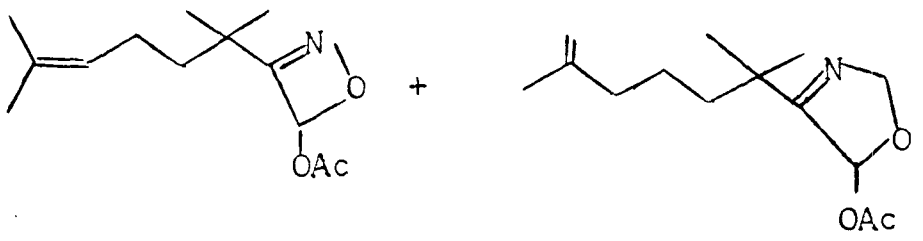
addition of acetic anhydride enhances the reaction rate. The addition of potassium acetate also enhances the reaction rate.

Just and Dahl[39] reported an oxidative cleavage reaction of 2,2,6-6 tetramethyl cyclohexanone oxime (CXII) with lead tetra acetate at low temperature in the presence of acrylate, which afforded adducts, isoxazolinyl acetates (CXIII - CXV).



(CXII)

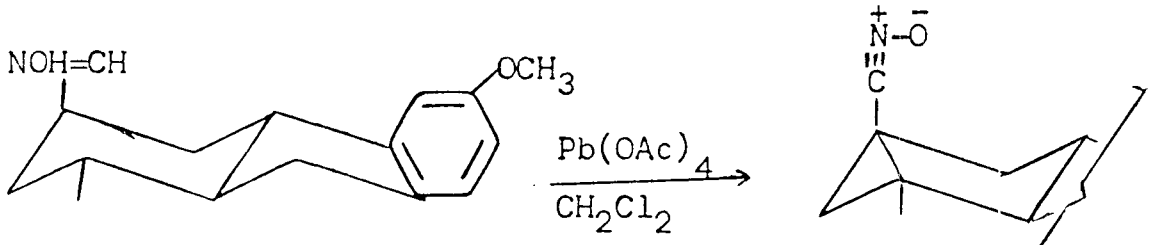
(CXIII)



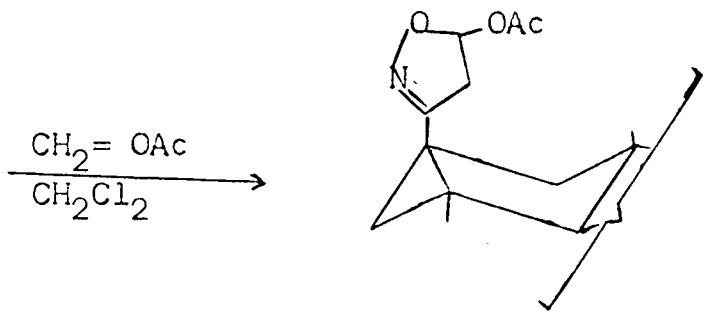
(CXIV)

(CXV)

Similarly oxidation of syn-o-methyl podocerpinalodoxime (CXVI) with lead tetraacetate in methylene chloride gave nitrile oxide (CXVII) which underwent 1,3-dipolar cycloaddition with vinyl acetate to afford 5-acetoxy-3(16-nor-O-methyl podocarp-β-yl) 2-isoxazoline (CXVIII)[40].

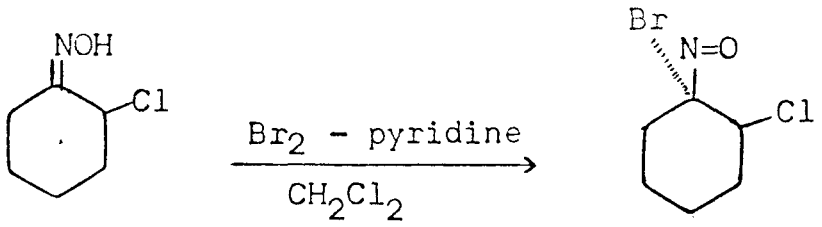


(CXVI) (CXVII)

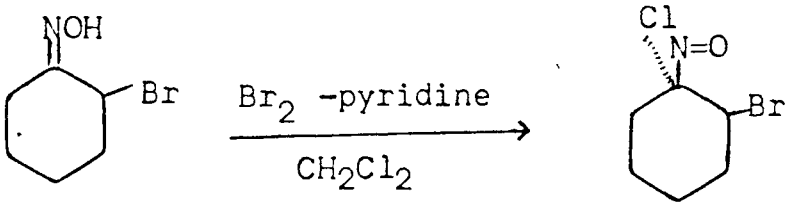


(CXVIII)

1-Bromo-1-nitroso-2-chlorocyclohexane (CXX) was obtained from 2-chlorocyclohexanone oxime (CXIX) with the reaction of pyridine and bromine in methylene chloride. Similarly 1-chloro-1-nitroso-2-bromocyclohexane (CXXII) was obtained from the oxime (CXXI) by passing chlorine gas into methylene chloride solution[41].

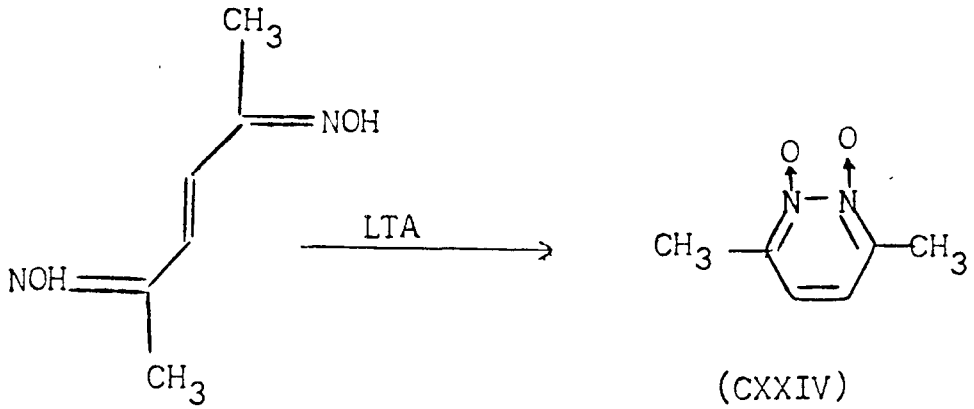


(CXIX) (CXX)

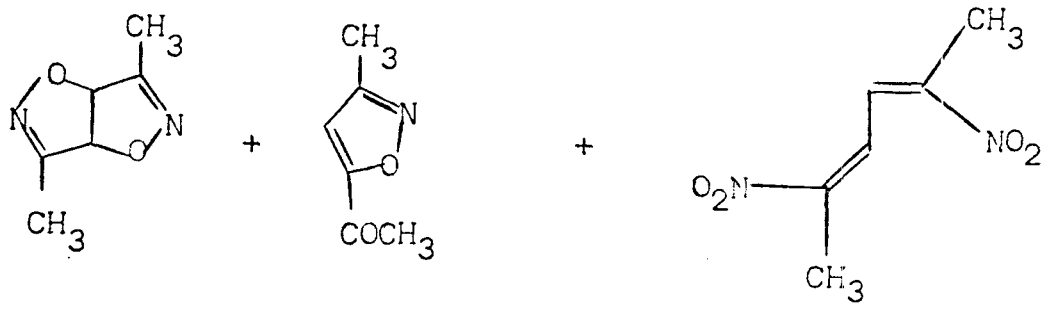


(CXXI) (CXXII)

Igeta et al.[42] reported that oxidation of 1,4-dimethyl-2-butene-1, 4-dione dioxime (CXXIII) with lead tetraacetate in methylene chloride gave 3,6-dimethyl pyridazine-1,2-dioxide (CXXIV), 3,6-dimethyl-3a, 6a-dihydro-isoxazole [5,4-d] isoxazole (CXXV), 5-acetoxy-3-methyl-isoxazole (CXXVI) and 2,5-dinitro-hexa-2,4-diene (CXXVII).

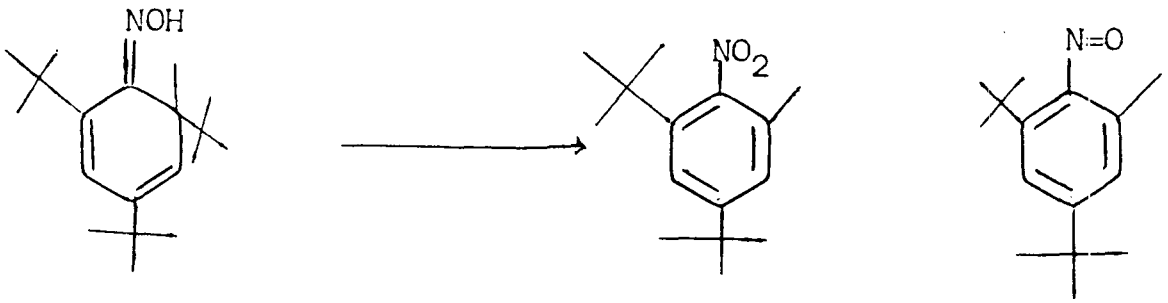


(CXXIV)

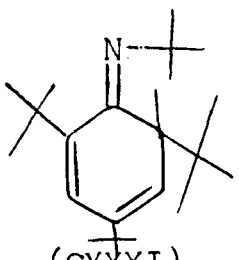


(CXXV) (CXXVI) (CXXVII)

In the same way oxidation of 1-hydroxyimino-6-methyl-2, 4,6-tri-t-butyl-2,4-cyclohexadiene (CXXVIII)[43] with silver oxide afforded 2,4-di-t-butyl-6-methylnitrobenzene (CXXIX), nitrosobenzene(CXXX) and 1-t-butoxyimino-2,4-6-tri-t-butyl-6-methyl-2,4-cyclohexadiene (CXXXI).

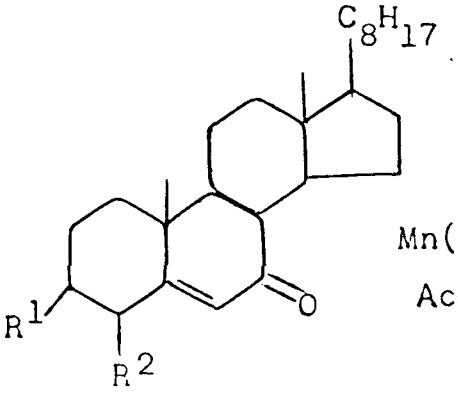


(CXXVIII) (CXXIX) (CXXX)

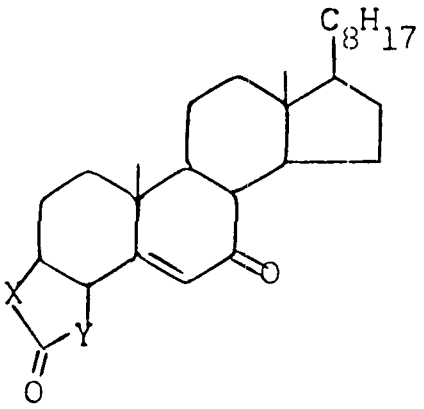


(CXXXI)

M.S. Ahmad et al.[44] reported the reaction of some α,β-unsaturated ketones from the cholestane series with Mn(III)acetate to afford γ-lactones (CXXXV, CXXXVI).



Mn(III)acetate
AcOH, Ac_2O



(CXXXII) $R^1 = R^2 = H$

(CXXXIII) $R^1 = Cl$, $R^2 = H$

(CXXXIV) $R^1 = H$, $R^2 = OAc$

(CXXXV) $X = CH_2$, $Y = O$

(CXXXVI) $X = O$, $Y = CH_2$

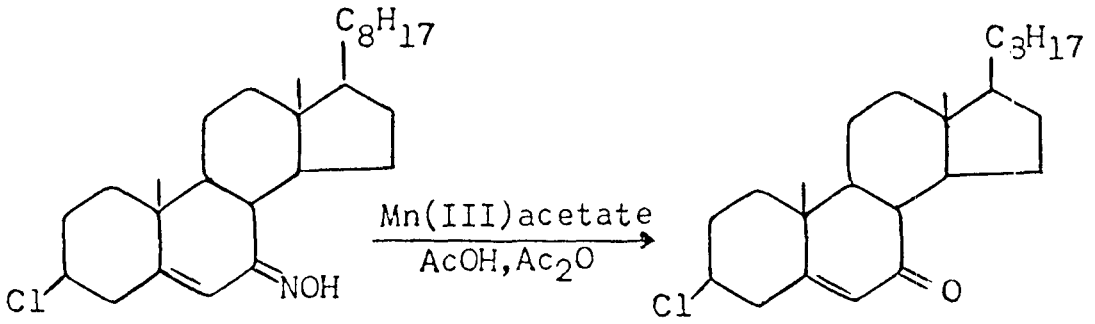
DISCUSSION

The oxidations of olefins lead to the formation of γ-lactone in most of the cases, in view of this fact, it is anticipated that steroidal unsaturated oximes might lead to some unknown hetero-steroidal compounds which may show biological activities. γ-Lactone moiety has attracted much synthetic interest[45] because of its occurrence in a wide variety of natural compounds having considerable biological activities as allergenic[46], growth inhibitor[47], anti-bacterial[48] and anti-tumor agents[49-52].

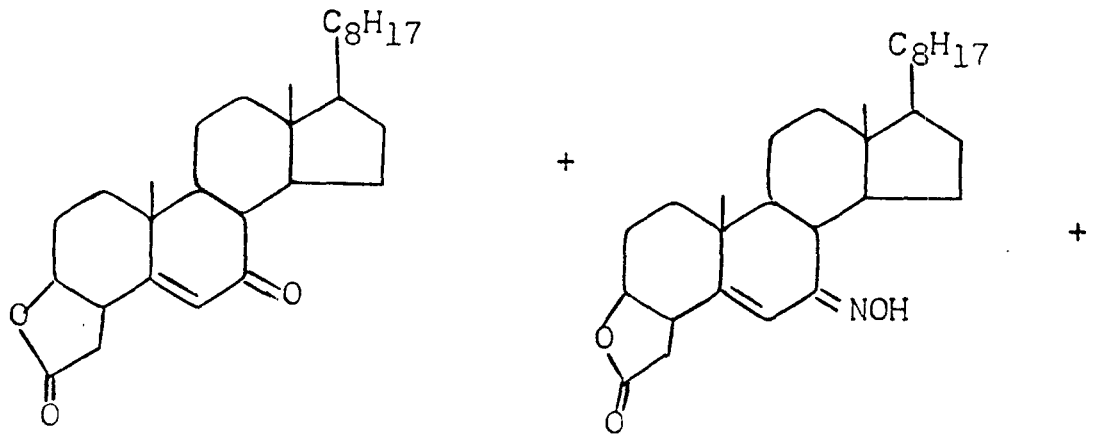
The survey of the literature on the use of Mn(III)acetate as well as the reactions of oximes revealed that no work has been reported so far on the reaction of oximes with Mn(III) acetate. A preliminary study is made, 3β-chlorocholest-5-en-7-one oxime (CXXXVII) was treated with Mn(III)acetate in acetic acid and acetic anhydride. The compounds obtained have been tentatively characterized on the basis of their elemental analysis, IR, NMR and chemical transformations.

Reaction of 3β-chlorocholest-5-en-7-one oxime with Mn(III) acetate in presence of acetic acid and acetic anhydride

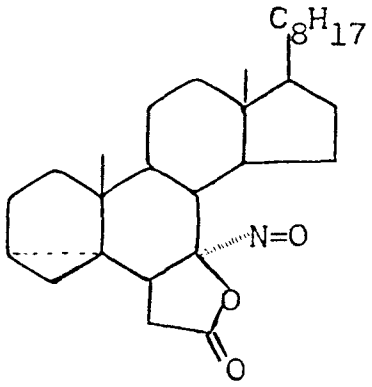
The reaction of 3β-chlorocholest-5-en-7-one oxime (CXXXVII)[53] with Mn(III)acetate in acetic acid and acetic anhydride after usual work up and column chromatography, provided four products, the solid m.p. 144° and 'Oil 1', 'Oil 2' and 'Oil 3'.



(CXXXVII) (CXXXVIII)



(CXXXVI) (CXXXIX)



(CXC)

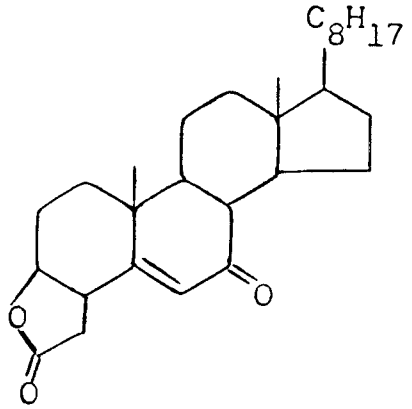
Characterization of the compound, m.p. 144° as 3β-chlorocholest-5 en-7-one (CXXXVIII)

The compound, m.p. 144°, analysed for $C_{27}H_{43}ClO$, was characterized as 3β-chlorocholest-5-en-7-one on the basis of its spectral properties and comparison with an authentic sample of 3β-chlorocholest-5-en-7-one (CXXXVIII)[54].

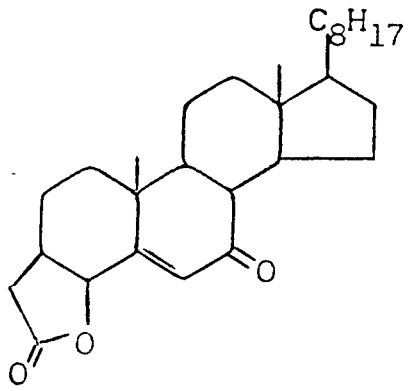
Characterization of the compound 'Oil 1' as 3β-hydroxy-7-oxo-cholest-5-en-4β-yl acetic acid γ-lactone (CXXXVI)

The compound analysed for $C_{29}H_{44}O_3$, the composition shows that this product could be the expected γ-lactone (addition of CH_2COO over the starting compound). The i.r. spectrum revealed the presence of a γ-lactone (1770 cm^{-1}), other i.r. values at 1670 cm^{-1}, 1630 cm^{-1}, 1225 and 1025 cm^{-1}. On this information several isomeric structures can be written (CXI - CXCVII). By the i.r. values the probable (CXCIII - CXCVI) structures with

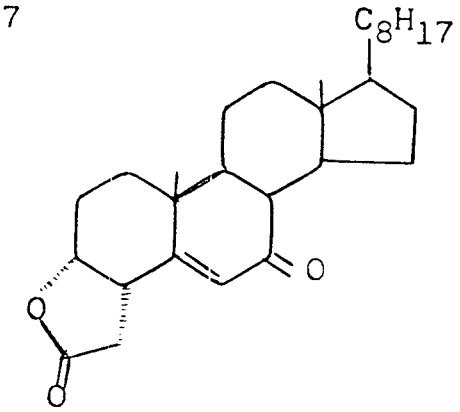
the same composition can be easily discarded due to the band at 1670 cm^{-1} for α,β-unsaturated carbonyl group. The band at 1630 cm^{-1} was attributed to C=C and C=O streching was obtained at 1225 and 1025 cm^{-1}. But these other four structures (CXCI, CXXXV, CXCII) can be written with equal plausibility on the elemental composition and i.r. data. The n.m.r. was helpful in choosing the correct structure for the molecule, which showed signals at ∂ 5.13 (me, $W\frac{1}{2}$ = 13Hz; $C_3\alpha$-H), ∂ 2.4 and 2.05 (4H, CH_2CO; $C_4\alpha$-H and $C_8\beta$-H). ∂ 1.25(C_{10}-CH_3), 0.69(C_{13}-CH_3), 0.9 and 0.81 for other methyl protons. The broad signal at ∂ 6.13 integratingfor one proton can be assigned to C6-proton, the small splitting of C6-proton was apparently due to long range coupling with C4α-H. The broad multiplet at 5.13 ($W\frac{1}{2}$ = 13Hz) clearly suggests that it is an axial proton having atleast one (a,a) coupling. This can best be accomodated with the (CXXXVI) and hence discarding the other isomeric structures (CXCI, CXXXV, CXCII). It is pertinent to mention that the compound is different from the sample of (CXXXV), in the n.m.r. spectroscopy. The above structure (CXXXVI) is supported by the fact that it is changed to the corresponding oxime (CXXXIX) by the reaction with NH_2OH-HCl, which is one of the product in the same reaction. Thus on the basis of above discussion, the compound 'Oil 1' may be characterized as 4β-hydroxy-7-oxo cholest-5-en-3β-yl acetic acid (CXXXVI).



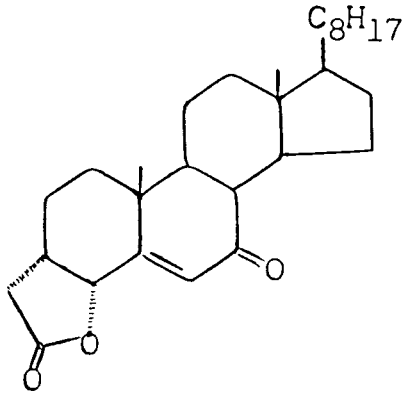
(CXXXVI)



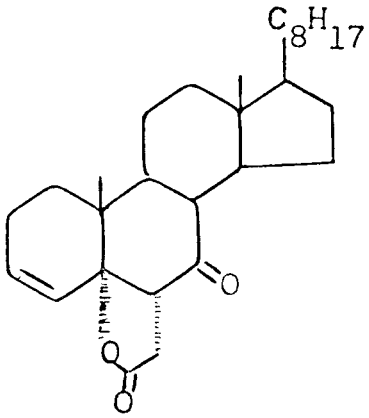
(CXXXV)



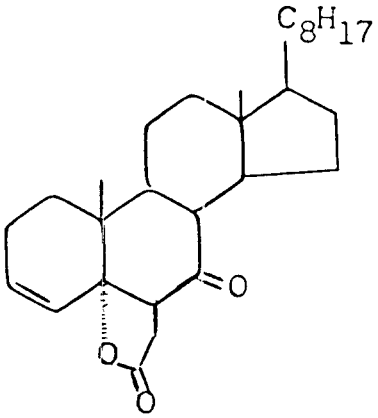
(CXCI)



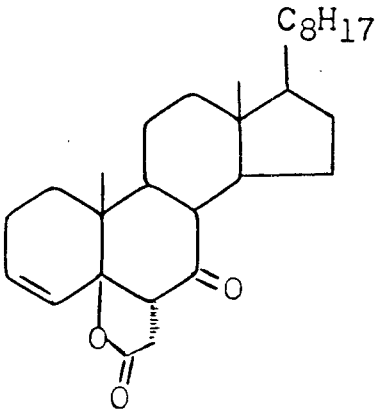
(CXCII)



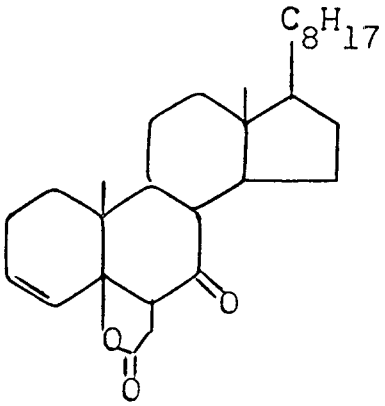
(CXCIII)



(CXCIV)



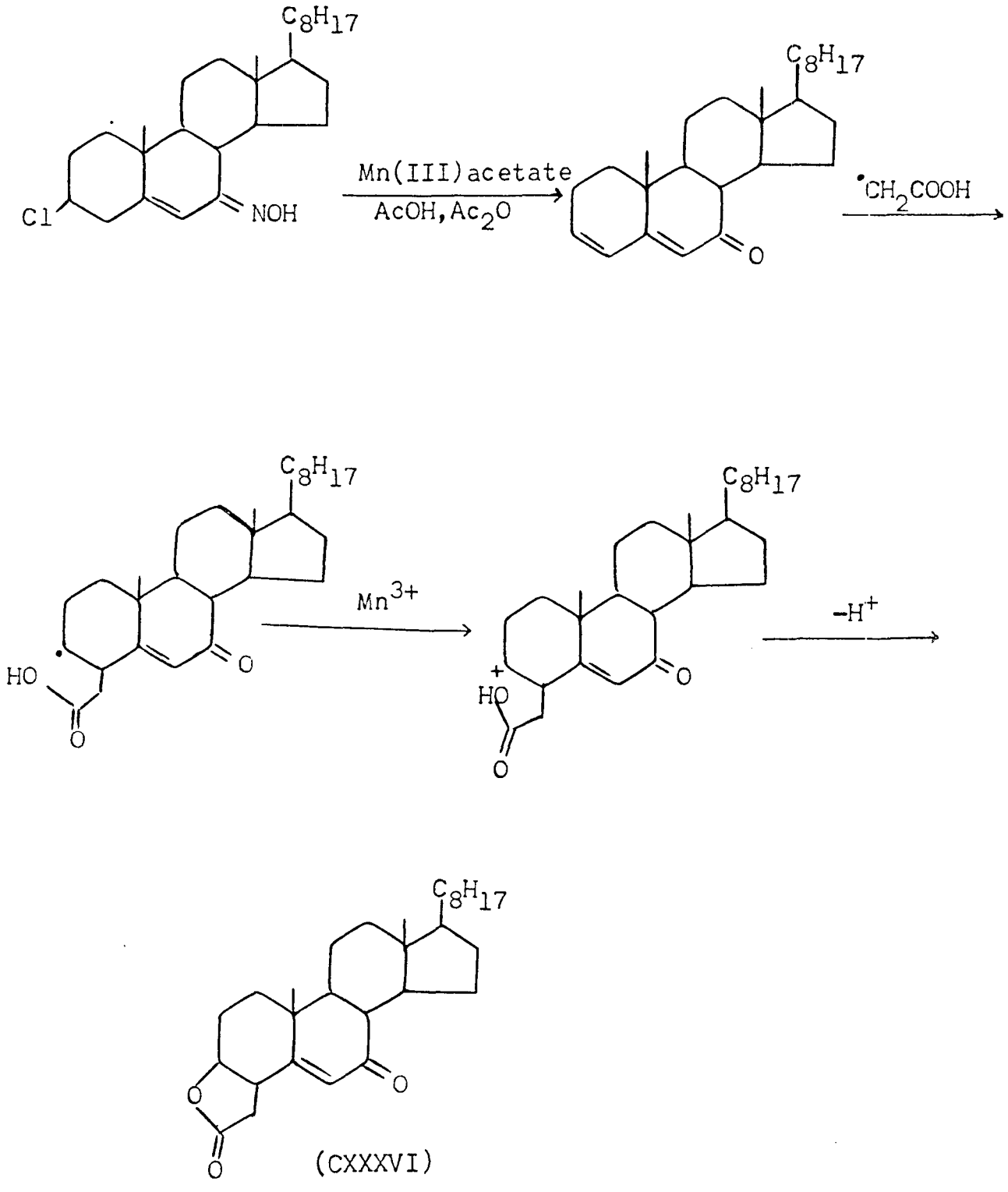
(CXCV)



(CXCVI)

A tentative pathway for the formation of (CXXXVI) from (CXXXVII) has been given in Scheme-2.

Scheme - 2



(CXXXVI)

Characterization of the compound 'Oil 2' as 3β-hydroxy-7-oximinocholest--5-en-4β-yl acetic acid γ-lactone (CXXXIX)

The oily compound analysed for $C_{29}H_{45}NO_3$. The i.r. spectrum exhibited bands at 3250 (N-OH), 1765 (C=O, γ-lactone), 1630 (C=C), 1520 (C=N) and also 1210, 1050 cm^{-1} indicating (C-O) stretching. The n.m.r. spectrum showed a singlet for one proton at δ 6.08, which was assigned to C6-vinylic proton. A broad signal integrating for one proton at δ 5.23 (mc, $W\frac{1}{2}$ = 14Hz, C3α-H). The peak at δ 2.16 showed the presence of (C_4α-H) (pseudo-equatorial). Another signal at δ 2.06 double doublet ascribable for γ-lactone methylene protons. The singlet was exhibited at δ 6.33 for N-OH (exchangeable with deuterium), other signal were observed at δ 1.25(C_{10}-CH_3), 0.68(C_{13}-CH_3) and remaining methyl protons at δ 0.9 and 0.8. It has been revealed that 'Oil 2' was also obtained, when 'Oil 1' was treated with $NH_2OH.HCl$. On the basis of above discussed spectral data and chemical transformations, the 'Oil 2' was characterized as 3β-hydroxy-7-oximinocholest-5-en-4β-yl acetic acid γ-lactone (CXXXIX).

Characterization of the compound 'Oil 3' as 3α-5—cyclo-7α-nitroso-cholestan-7β-hydroxy 6β-yl-acetic acid γ-lactone (CXC)

The compound analysed for $C_{29}H_{45}NO_3$. The i.r. spectrum

exhibited absorption bands at 1770, 1520, 1375, 1220, 1050 cm^{-1}. The absorption band at 1770 cm^{-1} is a clear indication of γ-lactone moiety in the molecule. The bands at 1520 and 1375 cm^{-1} showed (C-N = O) while at 1220 and 1050 for (C-O) stretching. The i.r. values suggests the presence of C-N=O and the γ-lactone function in the molecule. The n.m.r. spectrum showed peaks at δ 2.05 (doublet like), δ 1.25(C_{10}-CH_3), 0.67(C_{13}-CH_3), δ 0.9 and 0.8 other methyl protons. The signal at δ 0.4 characteristic of the cyclo propane ring. The n.m.r. spectrum devoid of any down field signal after δ 2.05 which can be attributed to the α-methylene protons of γ-lactone moiety. The nature of the signal as doublet like with small J. values, 4Hz suggested that the adjacent C6-proton is equatorially α-oriented, in case of axial (β-oriented) C_6-H, this signal was expected to show higher coupling constant. Although the n.m.r. is more in favour of β-orientation of the γ-lactone moiety, the stereochemistry is not yet ascertained and further work is needed. Thus on the basis of above discussion the compound may tentatively be characterized as 3α-5α-cyclo-7α-nitroso cholestan-7β-hydroxy-6β-yl acetic acid γ-lactone (CXC).

EXPERIMENTAL

All melting points are uncorrected, i.r. spectra were determined in nujol with a Perkin-Elmer 621 and Pye Unicam SP_3-100 spectrophotometers, n.m.r. spectra were run in $CDCl_3$ on a Varian A-60 D instrument with T.M.S. as internal standard, TLC plates were coated with silica gel G and sprayed with 20% aqueous perchloric acid, light petroleum refers to a fraction of b.p. 60-80°C. N.m.r. values are given in ppm (s=singlet, d=doublet, t=triplet, q=quartel, br=broad, umc=unresolved multiplet centred at, mc=multiplet centered at), i.r. values are given in cm^{-1} (s=strong, m=medium, w=weak).

3β-Chlorocholest-5-ene

Freshly prepared thionylchloride (40 ml) was added to cholesterol (50 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened, the reaction mixture was gently heated at a temperature 50-60°C on water bath for 1 hour, and then poured on crushed ice with stirring. The yellow solid thus obtained was filtered under suction, washed several times with water and dried, recrystallization from acetone gave cholest-5-en-3β-yl chloride (38 g), m.p. 94°(lit.[55], m.p. 96-97°).

3β-Chlorocholest-5-en-7-one (CXXXVIII)

A solution of t-butyl chromate from t-butyl alcohol (60 ml) Cro3 (20 g), acetic acid (84 ml) and acetic anhydride (10 ml) was added at $0^{o}C$ to a solution of 3β-chlorocholest-5-en (8 g) in carbon tetrachloride (150 ml), acetic acid (30 ml), acetic anhydride (10 ml). The contents were refluxed for 3 hours and then it was diluted with water. The organic layer was washed successively with sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure furnished an oil, which was crystallized from methanol gave ketone (CXXXVIII) (3.5 g) m.p. 144^{o} (lit.[56], m.p. $144-145^{o}$).

3β-Chlorocholest-5-en-7-one oxime (CXXXVII)

3β-Chlorocholest-5-en-7-one (CXXXVIII) (3 g), hydroxylamine hydrochloride (4 g) and sodium acetate trihydrate (3 g) were dissolved in ethanol (125 ml). The mixture was heated under reflux for 3 hours on water bath. The excess of the solvent was removed under reduced pressure and the residue was poured on to crushed ice. The crude oxime thus obtained was filtered under suction, washed with water and air-dried, recrystallization from methanol gave 3β-chlorocholest-5-en-7-one oxime (CXXXVII) m.p. 195^{o} (lit.[53], m.p. 197^{o}).

I.R. : 3294 (N-O<u>H</u>), 1645 (C=C-C=N), 1620 cm^{-1}(C=C); δ 7.89

(s, 1H, N-O<u>H</u>, exchangeable with D_2O), δ 6.76 (s, 1H, C_6-H, vinylic), 3.55 (m, 1H, $C_3\alpha$-<u>H</u>, axial, $W\frac{1}{2}$ = 22Hz), 2.8 (dd, 2H, C_4-<u>H</u>z), 1.15, 0.91, 0.83 and 0.71 (other methyl protons).

<u>Preparation of Mn(III) acetate</u>

Manganese (III) acetate dihydrate was prepared by modification of Christiansen's procedure[57]. Manganese (III) acetate tetrahydrate (24 g) in acetic acid (250 ml) was heated under reflux for 20 mts. The solution was cooled to just below the b.p. and then maintained under gentle reflux alongwith slow addition of potassium permanganate in portions (4 g). When the addition was complete the mixture was heated under reflux for 30 mts and cooled to room temperature, water (85 ml) was added. The dark solution was seeded with a little manganese (III) acetate and left for 16 hours. The einnaman coloured solid was filtered and recrystallized from aqueous 90% acetic acid. Idometric analysis indicated greater than 90% purity.

<u>Reaction of 3β-chlorocholest-5-en-7-one oxime with Mn(III) acetate: 3β-Chlorocholest-5-en-7-one (CXXXVIII) 3β-hydroxy-7-oxo cholest-5-en-4β-yl acetic acid γ-lactone (CXXXVI), 3β-hydroxy-7-oximino cholest-5-en-4β-yl acetic acid γ-lactone (CXXXIX) 3α,5-cyclo-7α-nitroso-5α-cholestan-7β-hydroxy-6β-yl acetic acid γ-lactone (CXC)</u>

A mixture of 3β-chlorocholest-5-en-7-one oxime (CXXXVIII)

(2 g), Mn(III) acetate (30 g), acetic acid (50 ml) and acetic anhydride (25 ml) was heated under reflux until the dark brown colour of Mn(III) acetate ion disappeared (2 hours). The reaction mixture was poured into water and extracted with ether, the ethereal layer was washed successively with water, sodium bicarbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Removal of the solvent gave oil ($\sim$1.7 g), which was chromatographed over silica gel (40 g). Elution with light petroleum gave the starting compound (CXXXVII) m.p. 197° (lit.[53], m.p. 197°).

Further elution with light petroleum - ether (15:1) gave the ketone (CXXXVIII) which was crystallized from methanol (165mg), m.p. 144° [56]. On the basis of m.p., m.m.p. and t.l.c. the compound can be identified as 3β-chlorocholest-5-en-7-one.

Further elution with light petroleum - ether (4:1) gave (CXXXVI) as a non-crystallizable 'Oil 1' (623 mg). ν_{max} 1770 (C=O, γ-lactone), 1670(α,β, unsaturated ketone), 1630 (C=C), 1225 and 1025 cm^{-1} (C-O). δ 6.13 (brs, 1H, C6-vinylic proton), 5.13 (mc, $W\frac{1}{2}$ = 13Hz, $C_3\alpha$-H), 2.4 and 2.05 (4H, CH_2CO;$C_4\alpha$-H and $C_8\beta$-H). 1.25 (C_{10}-CH_3), 0.69 (C_{13}-CH_3), 0.9 and 0.81 other methyl protons.

Analysis found : C, 78.81; H, 11.00

$C_{29}H_{44}O_3$ requires : C, 79.04; H, 10.06%.

Further elution with light petroleum - ether (10:1) provided (CXXXIX) as a non-crystallizable 'Oil 2' (832 mg). ν_{max} 3250 (N-OH), 1765 (C=O), γ-lactone), 1630 (C=O), 1520 (C=N), 1210 and 1015 cm^{-1} (C-O). δ 6.33 (s, NOH, exchangeable with D_2O), 6.08 (C_6-vinylic proton), 5.23 (mc, $W\frac{1}{2}$ = 14Hz, $C_3\alpha$-H), 2.16 (br, $C_4\alpha$-H), 2.06 (dd, $CH_2COO^{\bullet}$), 1.25 (C_{10}-CH_3), 0.68 (C_{13}-CH_3), 0.9 and 0.8 other methyl protons.

Analysis found : C, 76.13; H, 9.70; N, 3.01

$C_{29}H_{45}NO_3$ requires: C, 76.43; H, 9.95; N, 3.07%

Continued elution with the same solvent system (1:1) afforded (CXC) (325 mg) as a non-crystallizable 'Oil 3' ν_{max} 1770 (C=O, γ-lactone), 1520, 1375 (C-N=O), 1220 and 1050 cm^{-1} for (C-O). δ 2.05 (d, $CH_2COO^{\bullet}$), 1.25 (C_{10}-CH_3), 0.67 (C_{13}-CH_3), 0.9 and 0.8 other methyl protons, 0.4 (cyclopropane).

Analysis found : C, 75.71; H, 9.84; N, 3.00

$C_{29}H_{45}NO_3$ requires: C, 76.43; H, 9.95; N, 3.07%.

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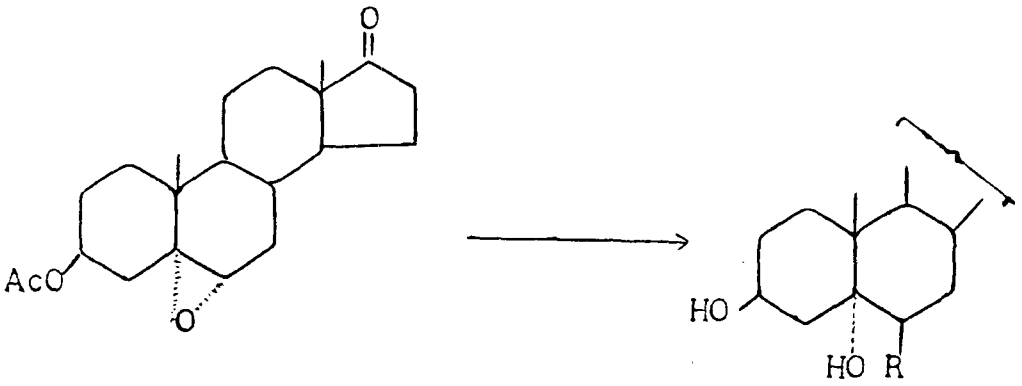
CHAPTER-TWO

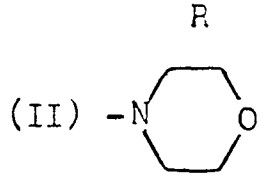
AMINOSTEROLS

THEORETICAL

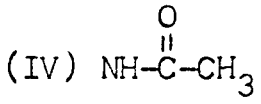
Hewett and Savage[1] reported the preparation of several amino sterols. 6β-Amino-5α-hydroxy-steroids were prepared from cleaving the corresponding 5α,6α-epoxides by reaction with ammonia or a primary or secondary amine. 3β-Acetoxy-5α,6α-epoxy androstan-17-one (I) was completely cleaved in three days by boiling with morpholine containing 10% water on give 3β,5α-dihydroxy-6β-morpholinoandrostan-17-one (II). The condensation of the epoxide (I) with boiling n-propylamine having 10% water or with ammonia in methanol and subsequent alkaline hydrolysis yielded 3β,5α-dihydroxy-6β-propylamino androstan-17-one (III). However, the epoxide (I) with a solution of ammonia in aqueous dioxan gave 6β-acetamido-3β, 5α-dihydroxy-androstan-17-one (IV). Acetylation of (IV) gave the diacetate (V).

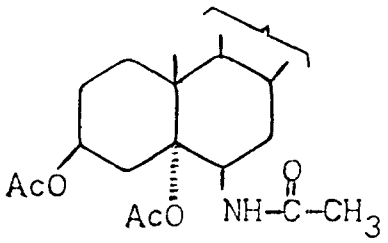


(I)



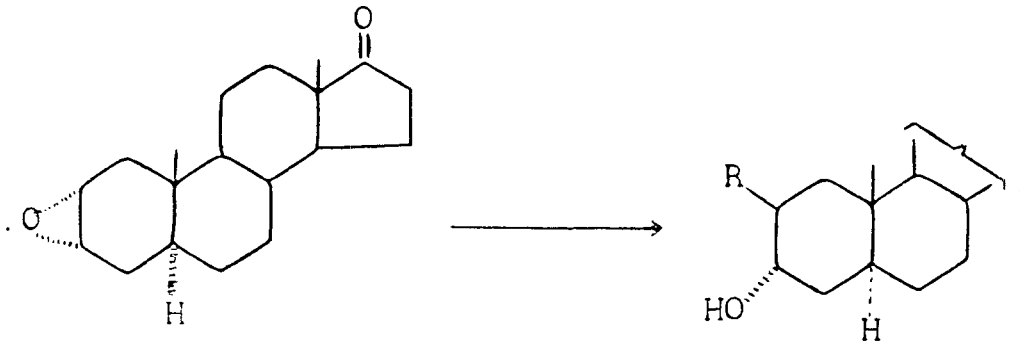
(III) $NH_2-CH_2-CH_2-CH_3$

(IV) 



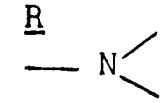
(V)

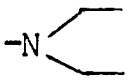
Condensation of 2α,3α-epoxy-5α-androstan-17-one (VI) with primary or secondary amine in the presence of water gave the corresponding 2β-amino-3α-hydroxy-5α-androstan-17-one (VII - XII). The reactions were catalysed by water possibly by the formation of more reactive intermediate oxonium ion[2].

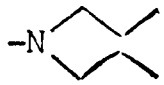


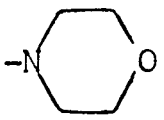
(VI)

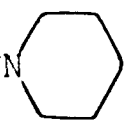
R

(VII) 

(VIII) 

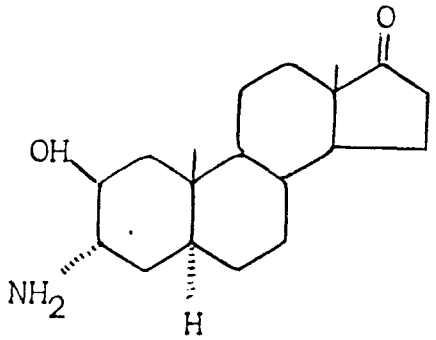
(IX) 

(X) 

(XI) 

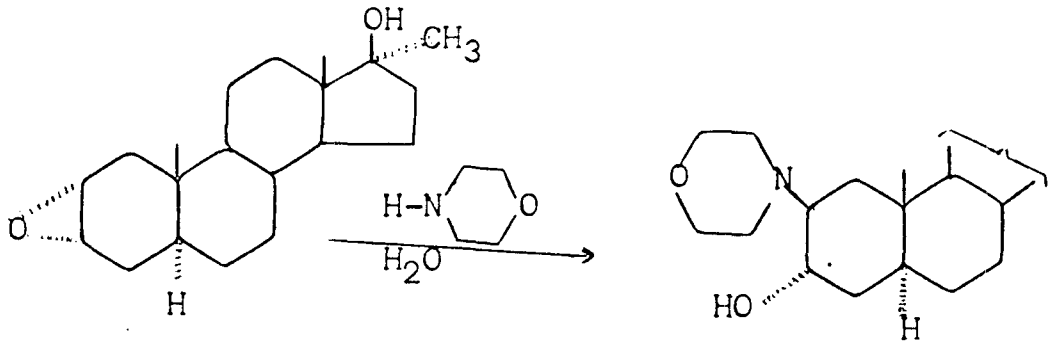
(XII) $-NH_2$

Hewett and Savage[2] gave the synthesis of 3α-amino-2β-hydroxy-5α-androstan-17-one (XIII), the hydrochloride of which was found to be novel anti-arrythmic drug[2].



(XIII)

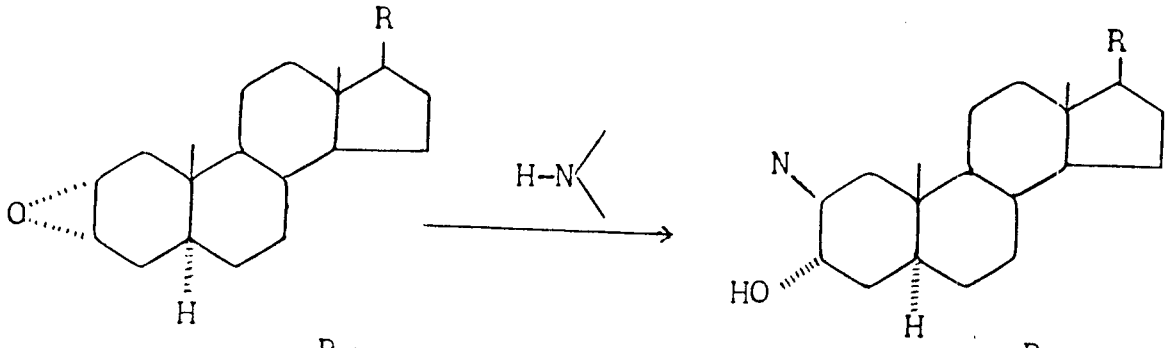
Condensation of 2α,3α-epoxy-17α-methyl-5α-androstan-17β-ol (XIV) with aqueous morpholine gave 17α-methyl-2β-marpholino-5α-androstan-3α-17β-diol (XV)[2].



(XIV) (XV)

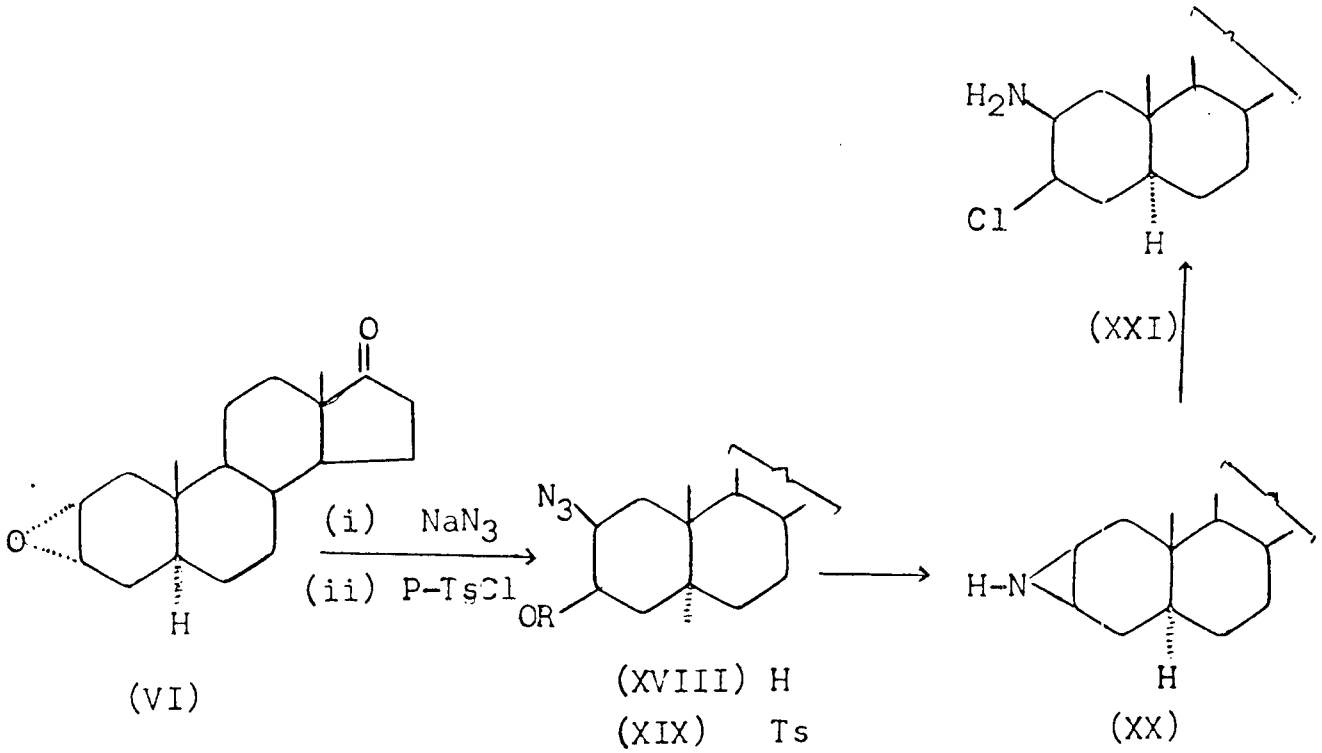
In the hope of potentiating the sedative activity[3] of 3α-hydroxy-2β-morpholino-5α-androstan-17-one (X), 11-oxo-group was introduced, which was found to enhanced the sedative potency and anesthetic activity[4,5].

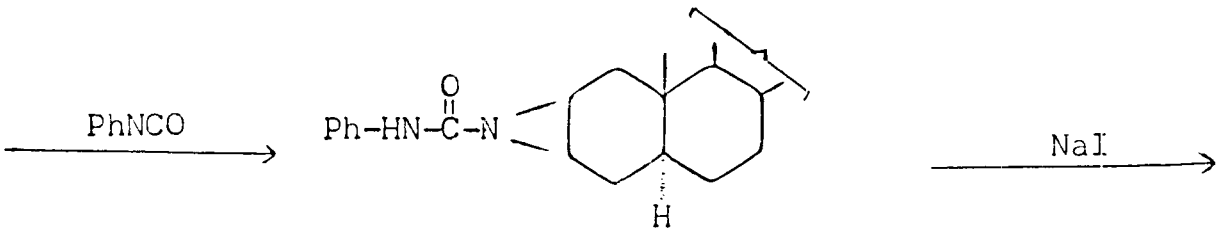
In 1961 Svoboda et al.[6] carried out the reaction of 2α, 3α-epoxy-5α-cholestane (XVI) and 2α, 3α-epoxy-5α-androstan-17-one (VI) with dimethylamine in order to obtain 2β-dimethylamino-5α-cholestane 3α-ol (XVII) and 2β-dimethylamino-3α-hydroxy-5α-androstan-17-one (VII), respectively.



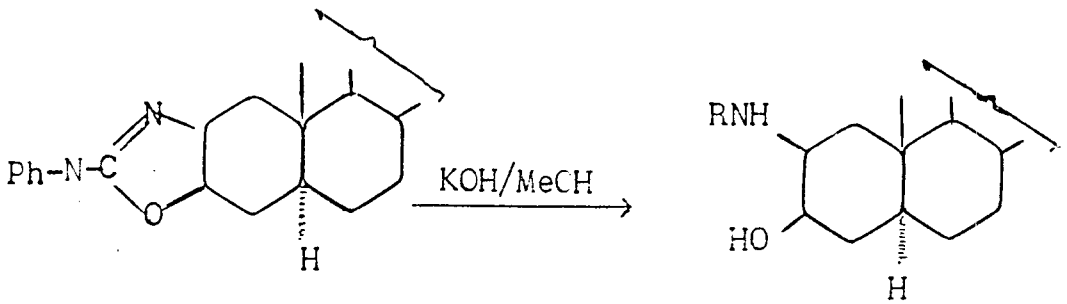
	R=		R=
(XVI)	C_8H_{17}	(XVII)	C_8H_{17}
(VI)	=O	(VII)	=O

Ponsold and Freibsch[7] synthesized 2β, 3β-imino-5α-androstan-17β-ol (XX) from 2α, 3α-epoxy-5α-androstan-17-one (VI) via the corresponding azidoalcohol tosylate (XIX). The aziridine (XX) was converted to thechloroamino androstane (XXI) and also to hydroxyamino androstanone (XXIV) through the intermediates (XXII) and (XXIII) as shown.



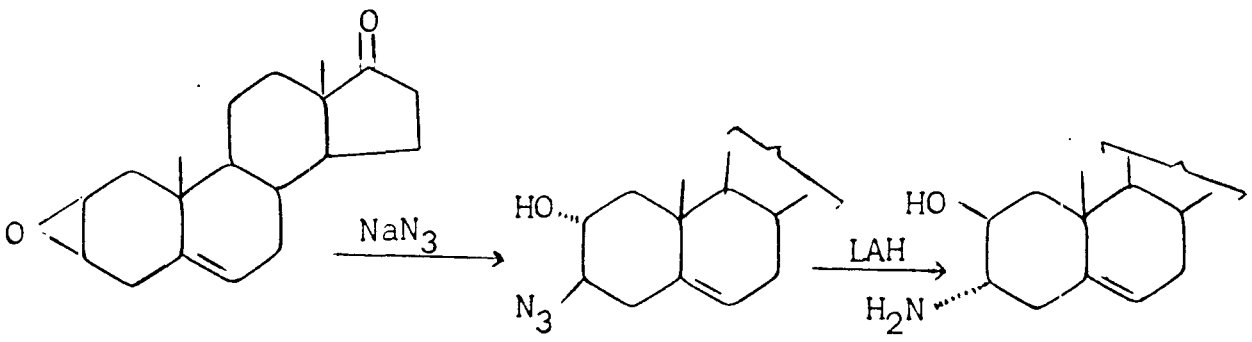


(XXII)

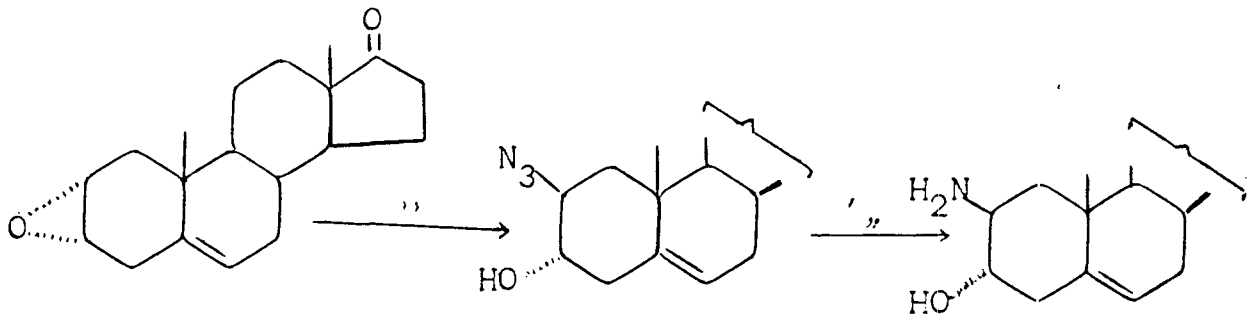


(XXIII) (XXIV)

Campbell et al.[8] reported the synthesis of 3α-amino-2β-hydroxyandrost-5-en-17-one (XXVII) and 2β-amino-3α-hydroxyandrost-5-en-17-one (XXX) from 2β, 3β-epoxy-androst-5-en-17-one (XXV) and its epimer (XXVIII), respectively.

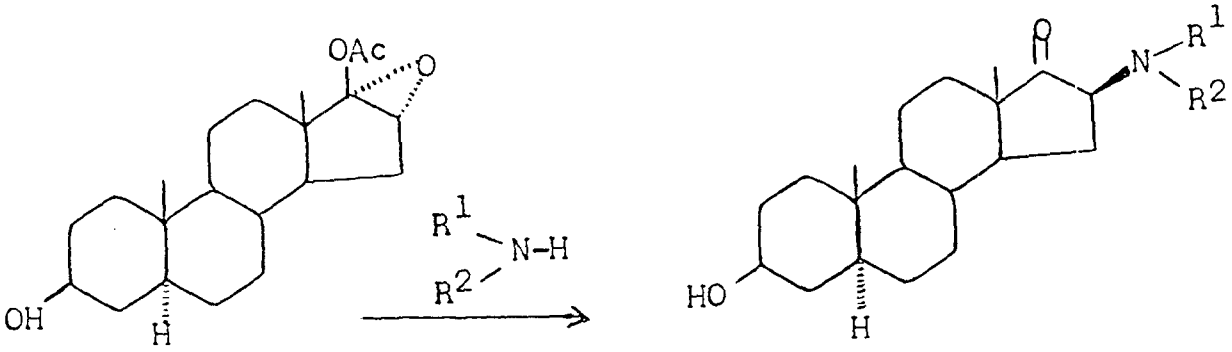


(XXV) (XXVI) (XXVII)



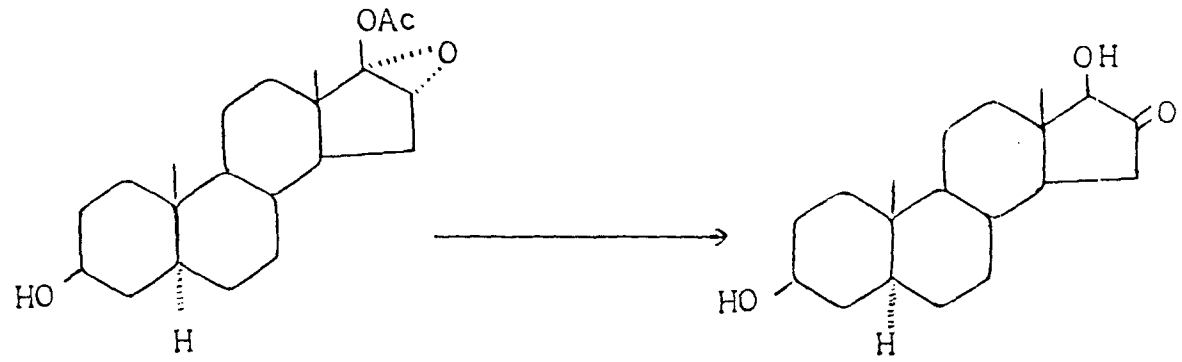
(XXVIII) (XXIX) (XXX)

Savage et al.[9] reported the synthesis of 16β-amino-17-oxo-steroid (XXXII) from 17β-acetoxy-3β-hydroxy-16α-17α-epoxy-5α-androstane (XXXI).

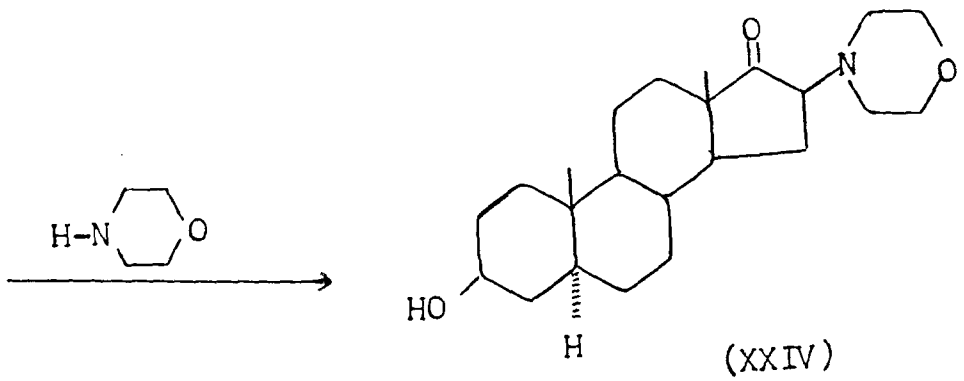


(XXXI) (XXXII)

Hewett and Savage[10] reported the 16β-morpholino-17-one (XXXIV) from the 17-β-acetoxy-16α-17α-epoxide (XXXI).

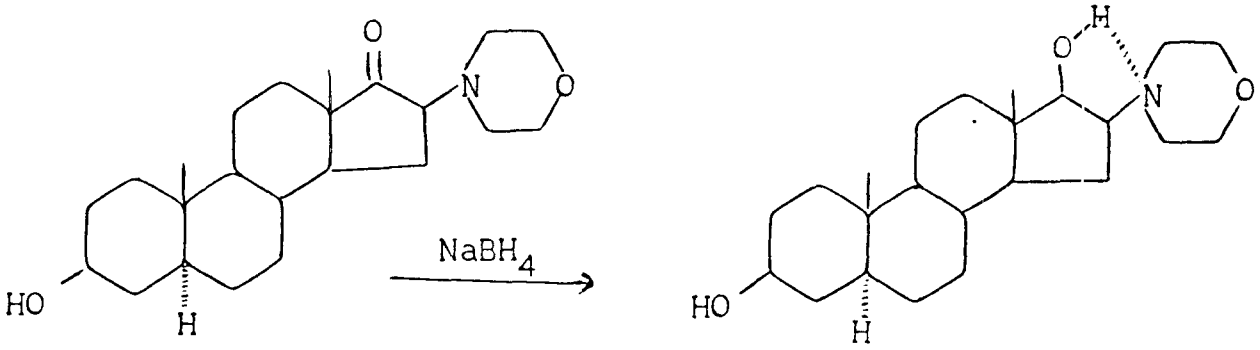


(XXXI) (XXXIII)



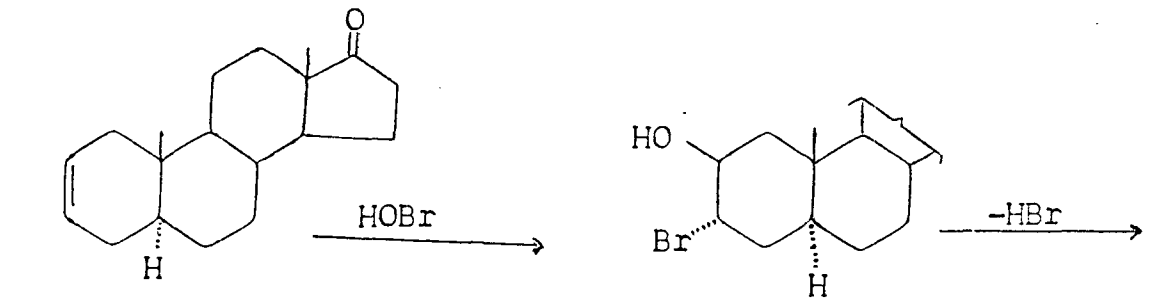
(XXIV)

Reduction of 16β-morpholino-17-ketone (XXXIV) with sodium borohydride gave in 16β-morpholino-17β-ol (XXXV), which showed hydrogen bonding between the 17β-hydroxy group and 16β-nitrogen atom[10].

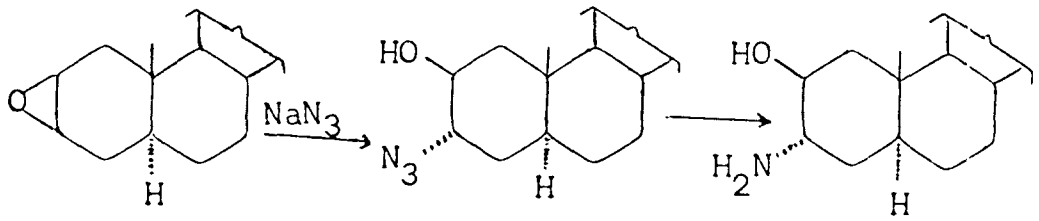


(XXXIV) (XXXV)

Campbell et al.[8] synthesized and evaluated the 3-amino-2-hydroxy and 2-amino-3-hydroxy isomers. The $\triangle^2$-17-ketone (XXXVI) was converted to 2β, 3β-epoxide (XXXVIII) via bromohydrin (XXXVII). Transdiaxial ring opening[11] of epoxide (XXXVIII) by sodium azide gave the sole product 2β-hydroxy-3α-azide (XXXIX), which was converted to amine (XL) by catalytic hydrogenation.

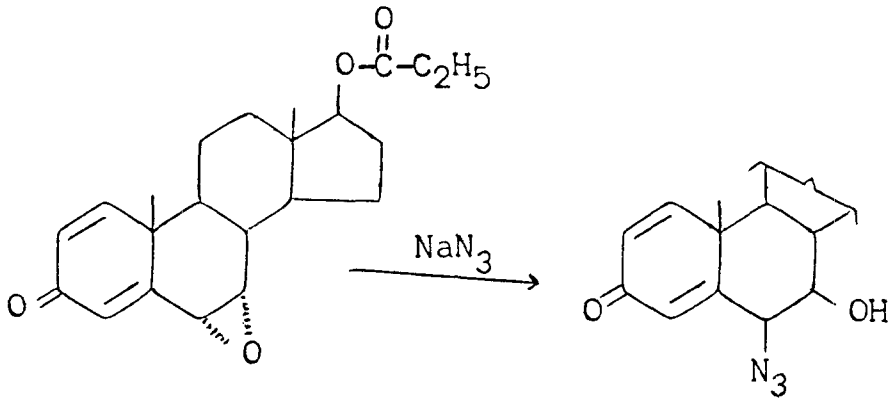


(XXXVI) (XXXVII)



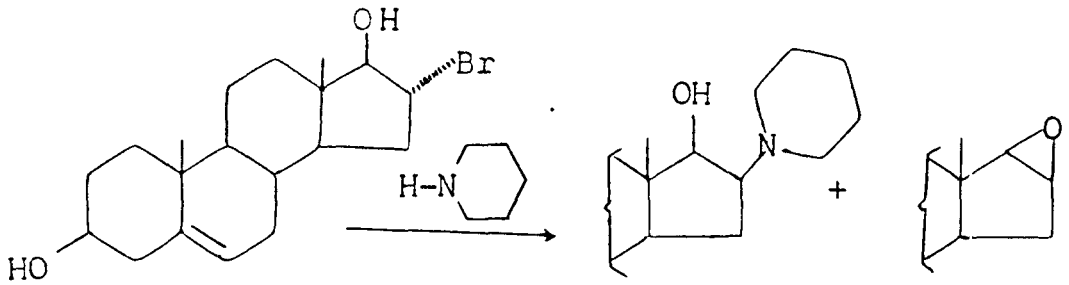
(XXXVIII) (XXXIX) (XL)

Kocor et al.[12] treated epoxy androstadienone (XLI) with NaN_3 in acetic acid at room temperature which gave azido-androstadiene (XLII) in 40% yield.



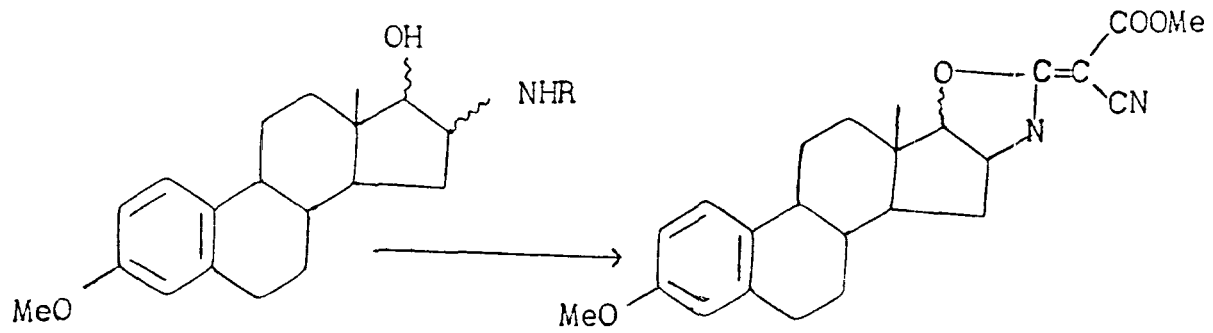
(XLI) (XLII)

Reaction of 16α-bromoandrost-5-en-3β,17β-diol (XLIII)[13] with piperidine, afforded 16β-piperidino-17β-hydroxy androst-5-ene (XLIV) along with the corresponding 16β, 17β, epoxide (XLV).



(XLIII) (XLIV) (XLV)

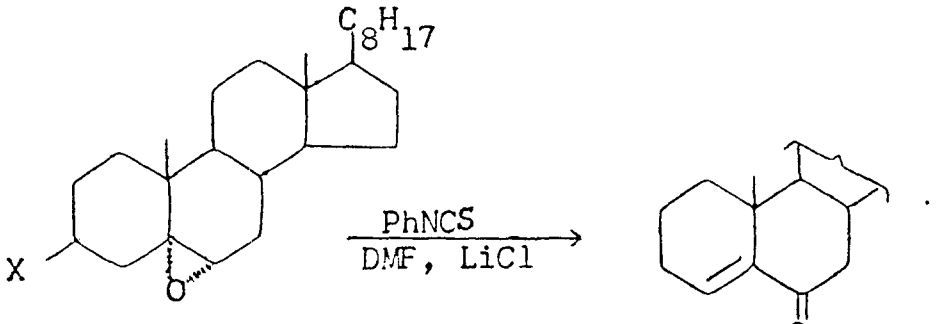
Molekularbiol and Shoenecker[14] reacted $(MeS)_2C{=}C(CN)-COOMe$ with (XLVI) to produce the derivative (XLVII) which gave a cyclic product (XLVIII). The reaction was stated to be used to study the configuration of vicinal aminoalcohols.



(XLVIII)

	R,
(XLVI)	H
(XLVII)	$-C(SCH_3){=}C(CN)-COOMe$

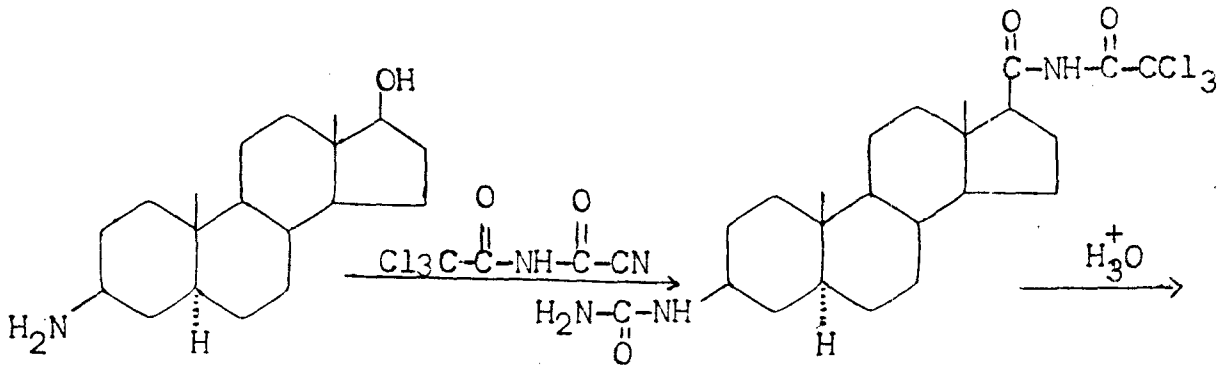
M.S. Ahmad et al.[15] identified the product cholest-4-6-one (LII) from 5,6α-steroidal epoxides (XLIX - LI). On reaction with phenylisocyanide in DMF.



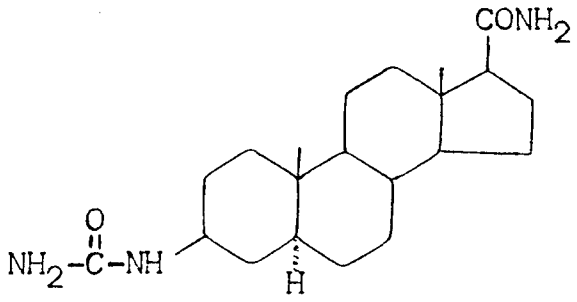
	X
(XLIX)	Cl
(L)	OH

(LII)

Treatment of 3β-amino-5α-androstan-17β-ol (LIII) with trichloroacetoisocyanate gave 3β-ureido-5α-androstan-17β-yl N-trichloroacetylcarbomate (LIV). Which was hydrolysed with acid to 3β-ureido-5α-androstan-17β-yl carbomate (LV). The overall yield from free base was 50 - 70%[16].

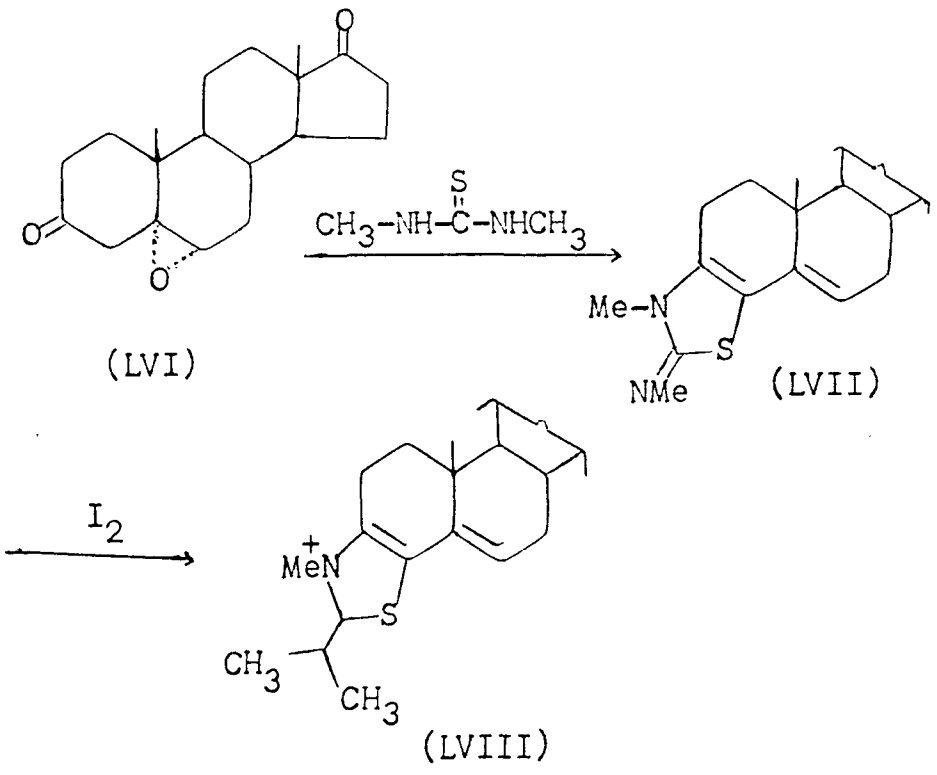


(LIII) (LIV)



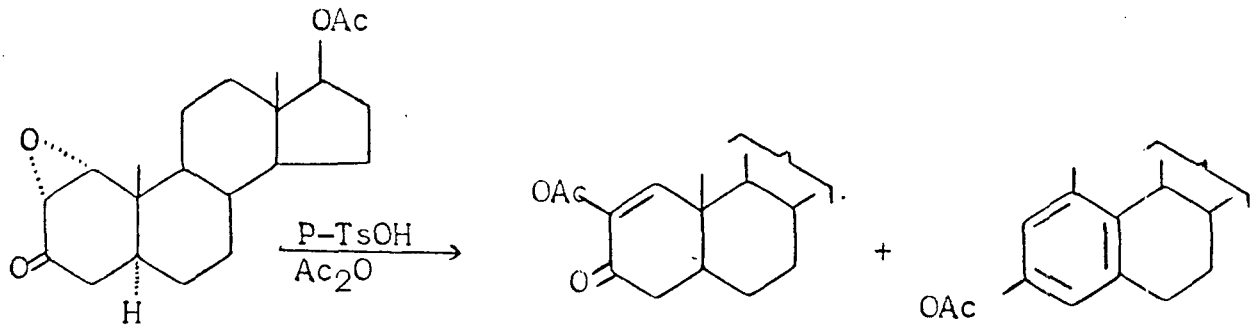
(LV)

4α,5 -epoxy-5α-androstane-3, 17-dione (LVI) when refluxed with N,N-dimethylthiourea gave 3,5-androstadieno [3,4-d] (2'-imino-3'-methyl) thiazoline (LVII), which was treated with iodide to give the quaternary salts (LVIII). Androstadieno-thiazoline have been shown[16] to posses contraceptive and antilopogenic activity and their quatarnary salts possesed antibacterial activity[17].



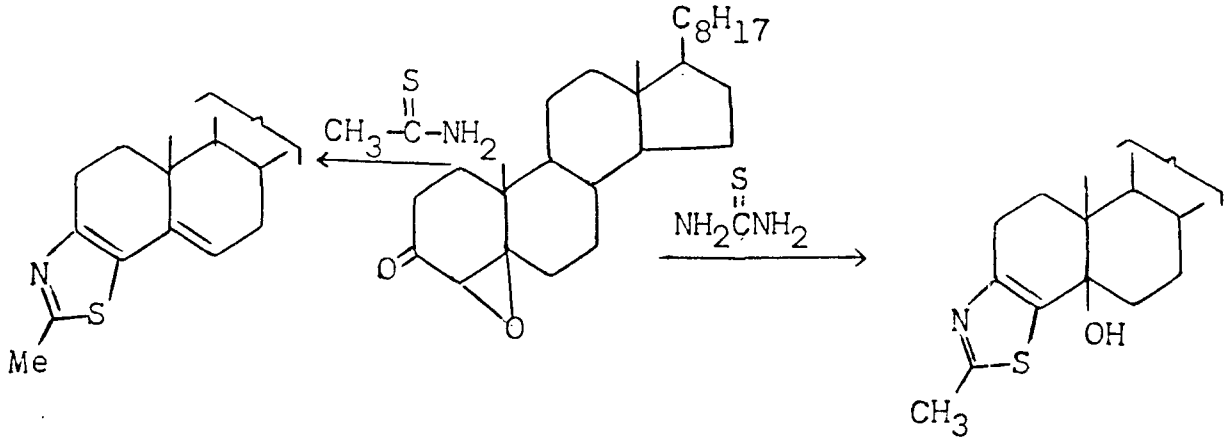
(LVI) (LVII) (LVIII)

17β-Acetoxy-1α,2α-oxido-5α-androstan-3-one (LIX)[18] when treated with p-toluene sulphonic acid and acetic anhydride afforded 2,17β-diacetoxy-5α-androst-1-en-3-one (LX) as the minor product and aromatic diacetate (LXI) as the major product.



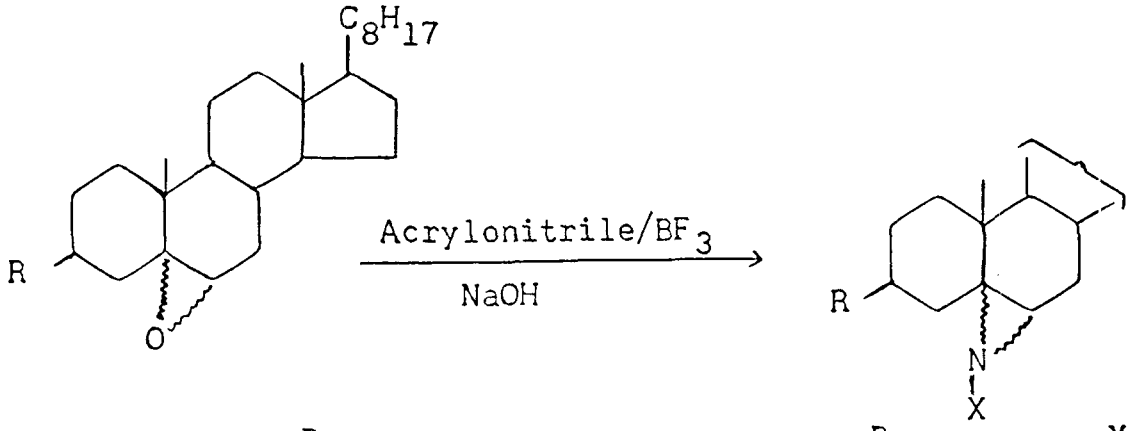
(LIX) (LX) (LXI)

M.S. Ahmad et al.[19] reported the formation of 3,5-cholestadieno [3,4-d]2'-methyl thiazole (LXIII) and 5β-hydroxycholest-3-eno [3,4-d] 2'-methylthiazole (LXIV) from 5β,6β-epoxy cholestan-3-one (LXII).



(LXIII) (LXII) (LXIV)

Shafiullah et al.[20,21] carried out the reaction of steroidal epoxides (XLIX, LXV, LXVI, LI) with acrylonitrile in presence of BF_3 and reported the formation of aziridine (LXVII - LXXII), respectively.



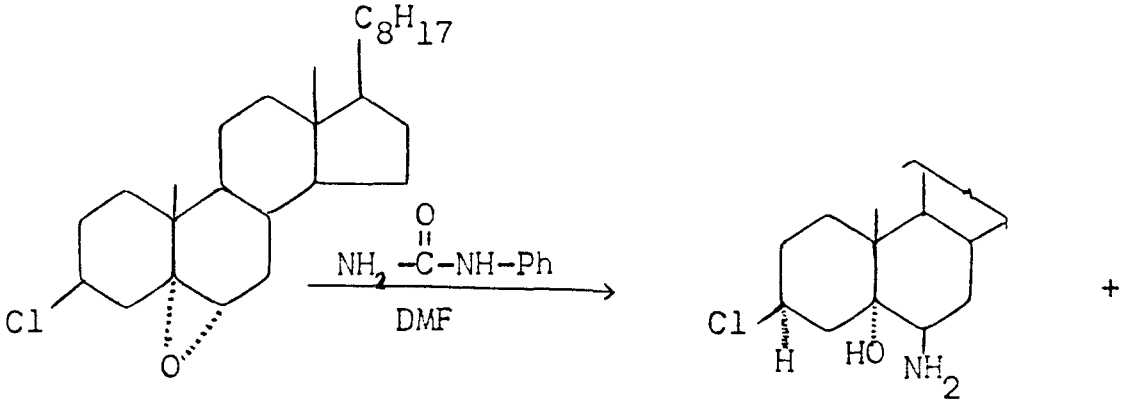
	R		R	X
(XLIX)	Cl, 5α,6α	(LXVII)	Cl,	$COCH_3$, 5β, 6β
(LXV)	Cl, 5β,6β	(LXVIII)	Cl,	$COCH_3$, 5α, 6α
(LXVI)	H, 5α,6α	(LXIX)	Cl,	$COCH(OH)CH_3$,5β,6β
(LI)	OAc, 5α,6α	(LXX)	H,	$COCH(OH)-CH_3$,5β,6β
		(LXXI)	OH,	$COCH(OH)CH_3$, 5β,6β
		(LXXII)	OAc,	$COCH(OH)CH_3$, 5β,6β

DISCUSSION

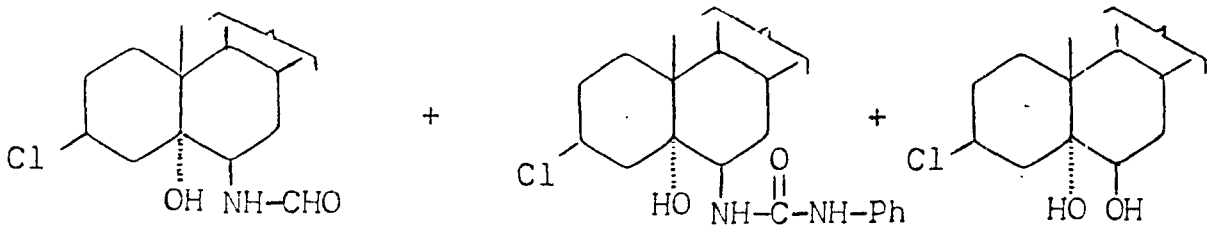
The synthesis of amino steroids due to their non-hormonal biological activities such as tranquilizing antiarrythmic, sedative and anaesthetic[22-29] has drawn the attention of organic chemists for last many years. The chapter deals with reaction of phenyl urea with some easily accessible steroidal epoxides. The substrates taken as a preliminary study are 3β-chloro-5,6α-epoxy-5α-cholestane (XLIX), 3β-hydroxy-5, 6α-epoxy-5α-cholestane (L), 3β-acetoxy-5, 6α-epoxy-5α-cholestane (LI).

Reactions of 3β-chloro-5,6α-epoxy-5α-cholestane (LXIX) with phenylurea

The epoxide (XLIX) was treated with phenylurea in dimethyl formamide under reflux conditions for 8 hrs. The reaction mixture after usual work up and column chromatography over silica gel, afforded four compounds, m.p. 173°, 157°, 220°, 125°.



(XLIX) (LXXIII)



(LXXXIV) (LXXV) (LXXVI)

Characterization of the compound, m.p. 173°, as 3β-chloro-5-hydroxy-6β-amino-5α-cholestane (LXXIII)

The compound m.p. 173°, showed molecular formula $C_{27}H_{48}NOCl$, (+ve -Beilstein test). The I.R. spectrum of the compound exhibited absorption peaks at 3570 and 3440 cm^{-1} for -OH and -NH groups. The N.M.R. spectrum displayed a broad singlet at δ 8.2 for -OH proton (exchangeable with deuterium). A multiplet at δ 3.38 was assigned to C6α-H ($W\frac{1}{2}$ = 6Hz) indicating that amino group was axial[30]. The presence of a brcad multiplet at δ 4.4 integrating for two protons was due to $-NH_2$. The C3α-H appeared at δ 4.2 as a multiplet ($W\frac{1}{2}$ = 17Hz). Methyl signals were seen at δ 1.2 ($C10-CH_3$), 0.7 ($C13-CH_3$), 0.73, 0.83 (other methyl protons). On the basis of the composition and spectral properties mentioned above the compound m.p. 173° can

be characterized as 3β-chloro-5-hydroxy-6β-amino-5α-cholestane (LXXIII).

Characterization of compound m.p. 151° as 3β-chloro-5-hydroxy 6β-amino-N-formyl-5α-cholestane (LXXIV)

The compound analysed for $C_{28}H_{48}O_2NCl$. The I.R. spectrum of the compound showed strong absorption band at 3440 cm^{-1} for -OH and -NH group. The band at 1700 cm^{-1} (amide I) indicated the presence of carbonyl group in the molecule. The formido group gave its characteristic absorption band at 1560 cm^{-1} (amide-II)[31], 760 cm^{-1} for C-Cl (+ve Beilstein test). The N.M.R. spectrum of the compound displayed a sharp singlet at δ 8.1 integrating for one proton ascribable to the formyl group. A multiplet for one proton was seen at δ 4.88 which could be assigned to -NH proton. A broad singlet at δ 2.0 was due to -OH proton which disappeared at D_2O shake. The multiplet for $C_3\alpha$-H and $C_6\alpha$-H appeared at δ 4.33. The methyl signals were observed at δ 1.15 (C_{10} -CH_3), 0.75 (C_{13} -CH_3), 0.9 and 0.85 (other methyl protons). On the basis of above evidences, the compound m.p. 151° can be characterized as 3β-chloro-5-hydroxy-6β-amino-N-formyl-5α-cholestane (LXXIV).

Characterization of the compound m.p. 220° as 3β-chloro-5, hydroxy-6β-amino-N-phenylamido-5α-cholestane (LXXV)

The compound m.p. 220° was analysed correctly for $C_{34}H_{53}N_2O_2$

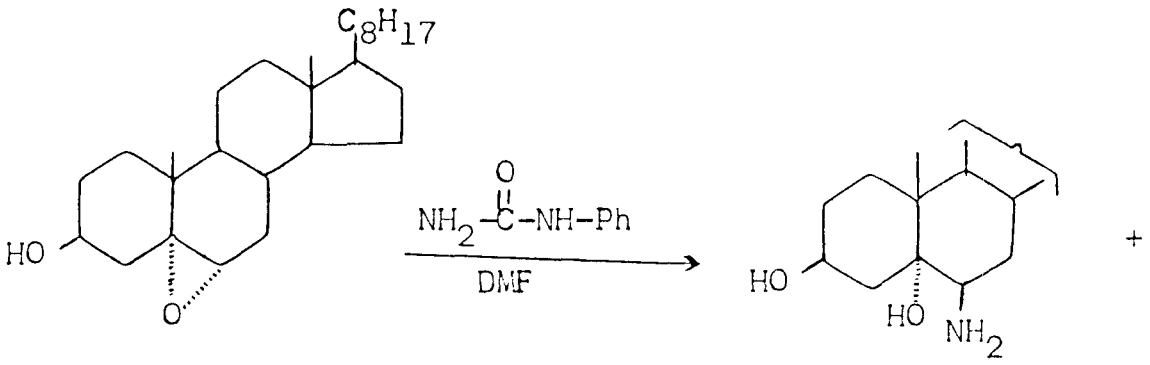
(+ve Beilstein test). The I.R. spectrum of the compound showed bands at 3300 and 3510 cm^{-1} for -OH and -NH groups. Amide group for phenylurea linkage was shown by bands at 1580 (amide-I) and 1540 (amide-II). The aromatic band appeared at 1640 cm^{-1}. The halogen was also indicated by a band at 750 cm^{-1}. The N.M.R. spectrum of the compound showed aromatic protons at ò 7.33. A multiplet at ò 5.33 ($W\frac{1}{2}$ = 18Hz), integrating for one proton was ascribed to $C_3\alpha$-H, another peak at 3.6 ($W\frac{1}{2}$ = 8Hz) assigned to $C_6\alpha$-H. Two peaks at ò 5.0 and ò 6.8 both integrating for one proton each could be assigned to (NH-CO-NHPh) and(-CO-NHPh), respectively. Hydroxy proton signal was seen at ò 2.1 as a broad singlet. The methyl protons gave singlets as ò 1.20, 0.9 0.85 and 0.75. On the basis of above discussion the compound has been tentatively characterized as 3β-chloro-5-hydroxy-6β-amino-N-phenyl amido-5α-cholestane (LXXV).

Identification of the compound m.p. 125° as 3β-chloro-5,6α-dihydroxy-5α-cholestane (LXXVI)

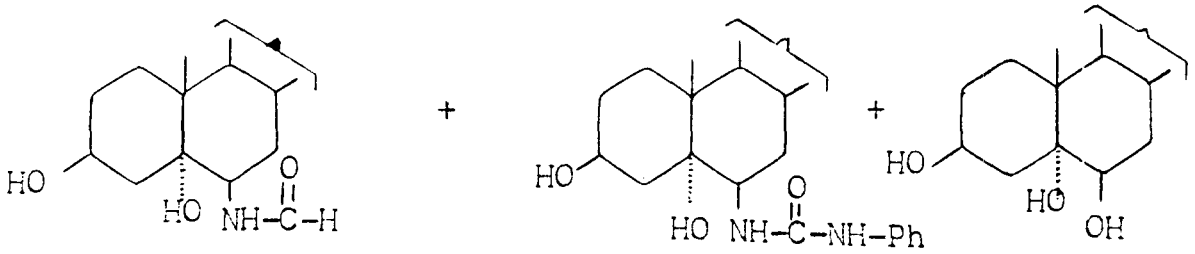
The compound m.p. 125° was analysed correctly for $C_{27}H_{47}O_2Cl$. The I.R. spectrum exhibited strong absorption band at 3450 cm^{-1} for -OH group. No other significant bands were observed in I.R. spectrum of the compound, m.p. 125°. The chemical and spectral values were compared and found identical with authentic sample of 3β-chloro-5, 6β-dihydroxy-5α-cholestane (LXXVI) (reported[32], m.p. 125 - 126°).

Reaction of 3β-hydroxy-5α,6α-epoxy-5α-cholestane (L) with phenylurea

The epoxide (L) was heated under reflux with phenyl urea in dimethylformamide for 8 hrs. The usual work up of the reaction mixture and column chromatography over silica gel provided four compounds m.p. 195°, oil, 135° and 244°.



(L) (LXXVII)



(LXXVIII) (LXXIX) (LXXX)

Characterization of the compound m.p. 195° as 3β,5-dihydroxy-6β-amino-5α-cholestane (LXXVII)

The compound m.p. 195° analysed correctly for $C_{27}H_{49}NO_2$. The I.R. spectrum of the compound exhibited strong bands at 3480 and 3300 cm^{-1} for OH and -NH groups along with other bands at 1290 and 1040 cm^{-1} for C-O . The N.M.R. spectrum of the compound exhibited a multiplet at δ 4.85 ($W\frac{1}{2}$ = 18Hz) for C3α-H. Another multiplet at δ 4.5 integrating for two protons was ascribed to $-N\underline{H}_2$. The C6α-H appeared as a multiplet at δ 3.6 and a broad singlet at δ 6.2 for -O<u>H</u>. Methyl signals were observed at δ 1.09 ($C10-C\underline{H}_3$), 0.65 ($C13-C\underline{H}_3$), 0.77 and 0.85 (other methyl protons). Thus on the basis of foregoing discussion the compound has been identified as 3β,5-dihydroxy-6β-amino-5α-cholestane (LXXVII).

Characterization of compound "oil" as, 3β,5-dihydroxy,6β-amino-N-formyl-5α-cholestane (LXXVIII)

The oil analysed correctly for $C_{28}H_{49}NO_3$. The I.R. spectrum of the compound showed strong absorption peak at 3470 cm^{-1} for OH and -NH groups. The band at 1700 cm^{-1}(amide-I) indicated the presence of a crabonyl group in the molecule. The formamido group gave its characteristic absorption bands at 1540 cm^{-1} (amide-II). The N.M.R. spectrum of the compound displayed a sharp singlet at δ 8.1 integrating for one proton of the formyl group. A multiplet for one proton was observed at

δ 4.9 which could be assigned to amide-NH. A broad singlet at δ 2.1 was ascribed to OH as it disappeared on D_2O shake. The signals for C3α-H and C6α-H merged at δ 4.2. The methyl signals were observed at δ 1.15 (C10-CH_3), 0.7(C13-CH_3), 0.9 and 0.83 (other methyl protons). On the basis of above evidences the compound is characterized as 3β-5α-hydroxy-6β-amino-N-formyl-5α-cholestene (LXXVIII).

Characterization of compound m.p. 135° as 3β,5-dihydro-6β-amino-N-phenylamido-5α-cholestane (LXXIX)

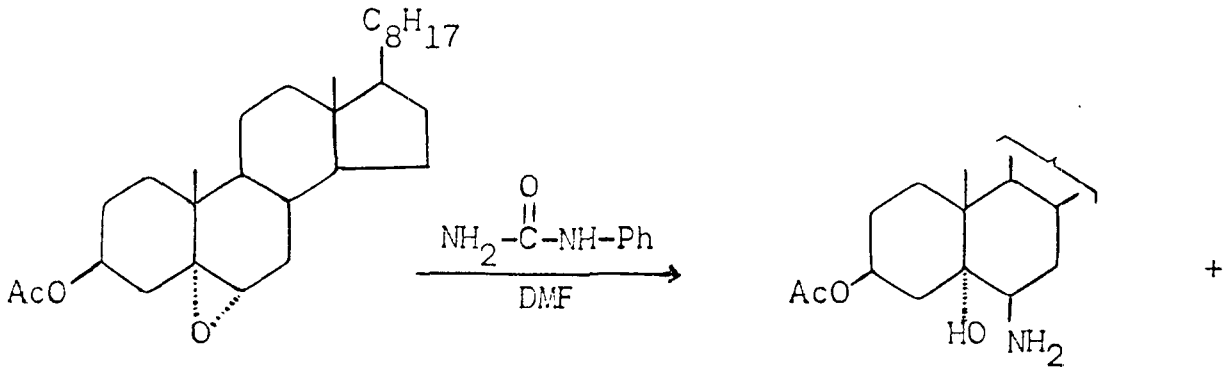
The compound m.p. 135° analysed for $C_{34}H_{54}N_2O_3$. The compound showed IR bands at 3550 and 3350 cm^{-1} for -OH and -NH group. Amide group, of phenylurea linkage was shown by bands at 1600 (amide-I) and 1540 cm^{-1} (amide-II). The aromatic band, appeared at 1650 cm^{-1}. The NMR spectrum of the compound showed signal for aromatic protons at δ 7.33. The multiplet at δ 5.3 integrating for one proton was ascribed to NH-CO.NHPh. The signal for C3α-H and C6α-H merged together and appeared as a multiplet at δ 3.5. Another multiplet at δ 6.5 integrating for one proton can easily be ascribed to NH-CONHPh. Hydroxy group gave a peak at δ 2.2 as a broad singlet, (disappeared on D_2O shake). Methyl signals were seen at δ 1.15 (C10-CH_3), 0.7 (C13-CH_3), 0.9 and 0.8 (other methyl protons). On the basis of above discussion the compound can be characterized as 3β,5-dihydroxy-6β-amino-N-phenyl-amido-5α-cholestane (LXXIX).

Identification of the compound m.p. 240° as 3β,5 ,6β-triol-5α-cholestane (LXXX)

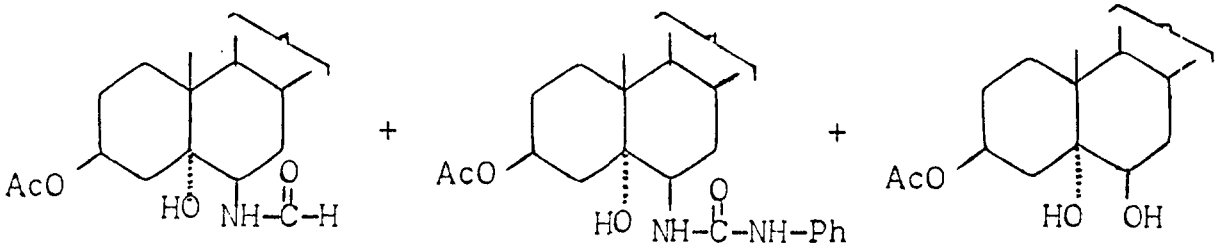
The compound m.p. 240° analysed for $C_{27}H_{48}O_3$. It was identified on the basis of spectral, elemental analysis and comparison with authentic sample of 3β,5 .,6β-triol-5α-cholestane (LXXX) (m.p., m.m.p. and t.l.c.) (reported[33], m.p. 237-239°).

Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (LI) with phenylurea :

The epoxide (LI) was heated under reflux with phenylurea in dimethylformamide for 8 hrs. The usual work up of the reaction mixture and column chromatography over silica gel provided, four compounds, m.p. 226°, 201°, 246°, 207°.



(LI) (LXXXI)



(LXXXII) (LXXXIII) (LXXXIV)

Characterization of compound m.p. 226° as 3β-acetoxy-5-hydroxy 6β-amino-5α-cholestane (LXXXI) :

The compound m.p. 226° was analysed for $C_{29}H_{51}NO_3$. It was identified on the basis of its spectral and elemental analysis and comparison with authentic sample of 3β-acetoxy-5-hydroxy-6β-amino-5α-cholestane (LXXXI) (m.p., m.m.p. and t.l.c.) (reported[34], m.p. 226-228°).

Characterization of the compound m.p. 201°, 3β-acetoxy-5-hydroxy-6β-amino-N-formyl-5α-cholestane (LXXXII) :

The compound m.p. 201° was analysed for $C_{30}H_{51}NO_4$. It was identified on the basis of its spectral, elemental analysis and comparison with authentic sample of the 3β-acetoxy-5-hydroxy-6β-amino-N-formyl-5α-cholestane (LXXXII) (m.p., m.m.p. and t.l.c.) (reported[34], m.p. 200-202°).

Characterization of compound m.p. 246° as 3β-acetoxy-5-hydroxy-6β-amino-N-phenylamido-5α-cholestane (LXXXIII) :

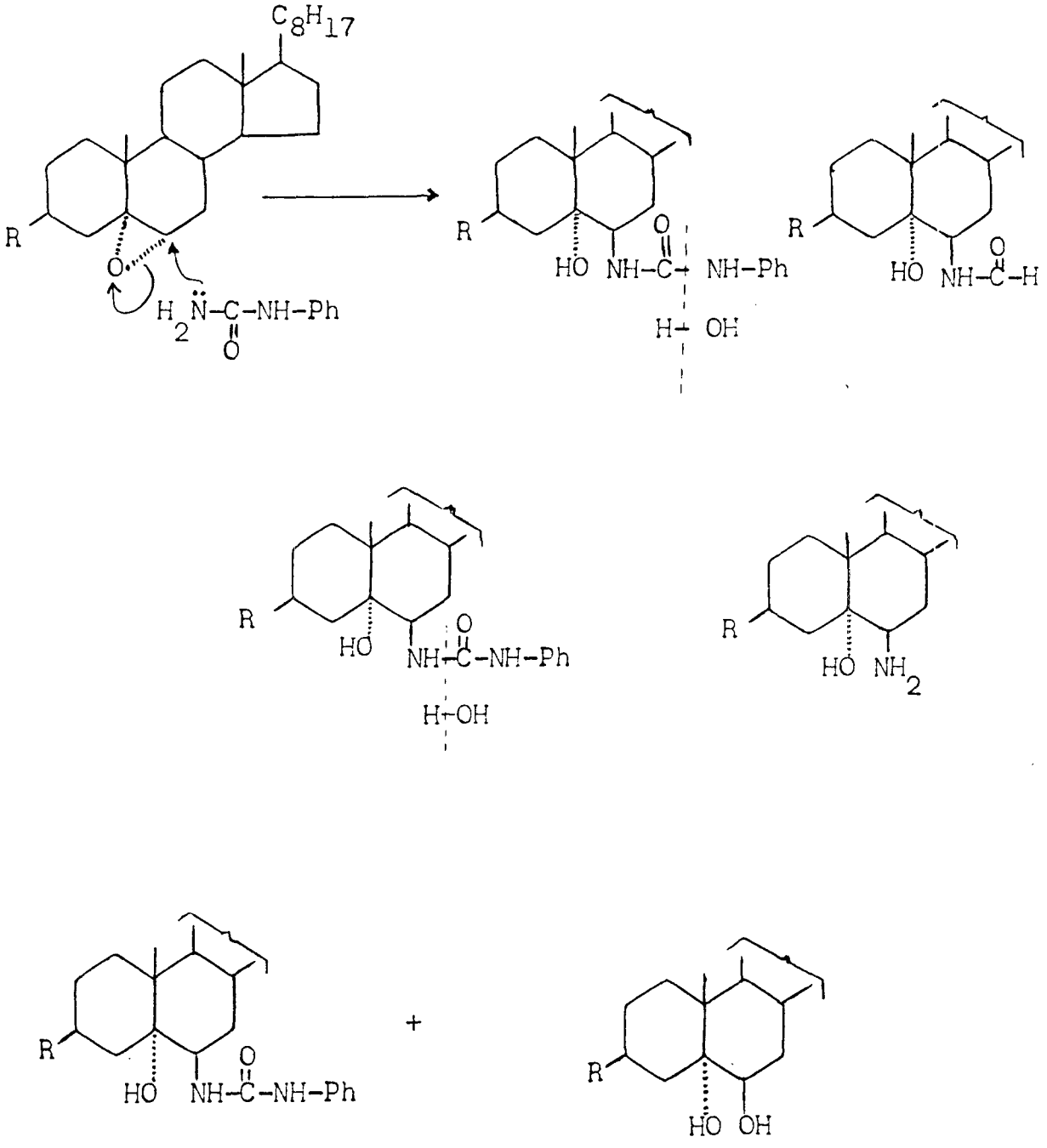
It was analysed for $C_{36}H_{56}N_2O_4$. The IR spectrum of the compound showed an absorption peak at 3440 cm^{-1} for (-OH and -NH). The amide (-NHCONHPh) function of the compound was indicated by a strong band at 1690 (amide-I) and 1515 (amide-II). The acetate

carbonyl was indicated by a band at 1730. The aromatic band was observed at 1640 cm^{-1}. On the basis of elemental analysis and i.r. values the compound is considered to be 3β-acetoxy-5, hydroxy-6β-amino-N-phenylamido-5α-cholestane (LXXXIII). The NMR spectrum is awaited for support to the structure proposed.

Characterization of compound m.p. 207° as 3β-acetoxy-5,6β-dihydroxy-5α-cholestane (LXXXIV) :

The compound m.p. 207° was identified on the basis of its spectral and elemental analysis and comparison with authentic sample of the diol (LXXXIV) (m.p., m.m.p. and t.l.c.) (reported[30], m.p. 209°).

The probable route for the formation of above discussed steroidal aminoalcohols has been shown in the following scheme.



EXPERIMENTAL

All m.p. are uncorrected. The I.R. spectra were determined in nujol with a Perkin-Elmer 237 spectrophotometer. NMR spectra were run in $CDCl_3$ on a Varian A 60 instrument with Me_4Si as the internal standard. T.L.C. plates were coated with silica gel (60-120 mesh). A 20% aqueous solution of perchloric acid was used as a spraying agent. Light petroleum refers to a fraction of b.p. 60-80° anhydrous sodium sulphate was used as the drying agent. N.M.R. values are given in ppm (s=singlet, d=doublet, dd=doublet doublet, br=broad, mc=multiplet centered at).

3β-Chloro-5,6α-epoxy-5α-cholestane (LXXIII)

Cholesteryl chloride[35] (11 g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mole equiv.) in chloroform and left at -8° for 20 hrs. The mixture was then washed with icecooledsodium bicarbonate solution (5%), water and sodium thiosulphate solution (5%) and again with water. Evaporation of the solvent gave an oil, which was crystallized from acetone to give (LXXII) as needles (8.1 g), m.p. 89° (reported[32], m.p. 89-90°).

3β-Hydroxy-5,6α-epoxy-5α-cholestane (L)

Cholesterol (11 g) was dissolved in chloroform (100 ml) and

treated with a solution of perbenzoic acid (1.1 mole equiv.) in chloroform and left at -8° for 20 hrs. The mixture was then washed with ice cooled sodium bicarbonate solution (5%), water and sodium thiosulphate solution (5%) and again with water. Evaporation of the solvent yielded (L) as an oil which was crystallized from acetone as needles (8.0 g), m.p. 139° (reported[36], m.p. 140°).

3β-Acetoxy-5,6α-epoxy-5α-cholestane (LI)

Cholesteryl acetate (11 g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mole equiv.) in chloroform and left at -8° for 20 hrs. The reaction mixture was then washed with ice cooled water, sodium bicarbonate solution (5%), water and sodium thiosulphate solution (5%) and again with water. Evaporation of the solvent provided (LI) as semi-solid which was crystallized from acetone as needles (8.4 g), m.p, 97° (reported[30], m.p. 97°).

PHENYLUREA

Dissolve (65 g) (0.5 mol) of aniline hydrochloride and (120 g) (2 mol) of urea in 200 ml of water contained in a 1 litre round bottom flask, filter the solution, if nacessary. Add 4 ml of concentrated hydrochloric acid and 4 ml glacial acetic acid. Fit the reflux condensor for 30 minutes. Fine

white crystals (diphenylurea) appear after 15 minutes and gradually increase in amount as the refluxing is continued. Cool the flask in icecoold water and filter with suction. Seperate the mixture of phenylurea and diphenylurea by boiling with 500 ml of water and filter while hot, residue in crude diphenylurea (m.p. 241°C). The filtrate on cooling gives crystalline solid, which is recrystallized from hot water to give phenylurea (30 g) (reported[37], m.p. 241°).

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (LXIX) with phenyl urea : 3β-Chloro-5-hydroxy-6β-amino-5α-cholestane (LXXIII), 3β-chloro-5-hydroxy-6β-amino-N-formyl-5α-cholestane (LXXIV), 3β-chloro-5-hydroxy-6β-amino-N-phenylamido-5α-cholestane (LXXV) 3β-chloro-5,6α-dihydroxy-5α-cholestane (LXXVI)

The mixture of 3β-chloro-5,6α-epoxy-5α-cholestane (XLIX) (2.5 g) and phenylurea (2 g) (1.5 mol) was dissolved in diemthyl formamide (100 ml) and heated under reflux for 8 hrs. The reaction was monitored by t.l.c. and after completion of the reaction, the reaction mixture was poured in water, and washed with sodium bicarbonate 5% and again with water and dried over anhydrous sodium sulphate. The solvent evaporation over water bath yielded a residue which was column chromatographed over silica gel (75 g). Each fraction of 25 ml was taken. Elution with light petroleum - ethyl acetate (75:1) provided a solid, which was recrystallized from light petroleum to give 3β-chloro-5-hydroxy-6β-amino-5α-cholestane (LXXXIII)

(LXXIII) (380 mg) with (75:1) light petroleum - ethylacetate which was recrystallized from light petroleum, m.p. 173°.

Analysis found : C, 80.37; H, 12.16; N, 3.45

$C_{27}H_{49}NOCl$ requires: C, 80.39; H, 12.15; N, 3.47%

IR ν_{max} 3570(-OH), 3440(-NH), 1280 and 1040(C-O), 730 cm^{-1}(C-Cl).

^1H N.M.R. δ 8.2(br, s, -OH, exchangeable with D_2O), 3.38(C6α-H, $W\frac{1}{2}$ = 6Hz), 4.4(NH_2), 4.2(m, C_3α-H, $W\frac{1}{2}$ = 17Hz), 1.2 (C_{10}—CH_3), 0.7 (C_{13}—CH_3), 0.73and 0.83 (other methyl protons).

Further elution with light petroleum - ethylacetate gave 3β-chloro-5-hydroxy-6β-amino-N-formyl 5α-cholestane (LXXIV) (200 mg) m.p. 151°.

Analysis found : C, 71.25; H, 10.30; N, 3.01

$C_{28}H_{48}O_2NCl$ requires: C, 72.25; H, 10.32; N, 3.10%

IR : ν_{max} 3440 (-OH, -NH), 1700 (amide-I), 1560 cm^{-1} (amide-II) and 760 cm^{-1} (C-Cl).

^1H-N.M.R. : δ 8.1 (formyl group , -CHO), 4.88 m(-NH), 4.33(m,2H, C_3β-H and C_6α-H), 2.0 (-OH), 1.15 (C_{10} -CH_3) 0.75(C_{13}—CH_3), 0.95 and 0.85 (other methyl group protons).

Further elution with light petroleum - ethylacetate (1:1)

gave 3β-chloro-5-hydroxy-6β-amino-N-phenyl amido 5α-cholestane (LXXV), which was recrystallized from light petroleum (250 mg) m.p. 220°.

Analysis found : C, 73.04; H, 8.6; N, 5.1

$C_{34}H_{53}O_2N_2Cl$ requires: C, 74.05; H, 8.71; N, 5.08%.

IR ν_{max} 3300 (-OH), 3510 (-NH), 1580 (amide-I), 1540 (amide-II), 1640 (benzene ring) and 750 cm^{-1} (C-Cl).

^1H N.M.R. δ 7.33 (aromatic protons), 6.8 (m, -NH-Ph), 5.0 (br —NH-C(=O)-) 5.33 (m $C_3\alpha$-H, $W\frac{1}{2}$ = 14Hz), 3.6 (m $C_6\alpha$-H, $W\frac{1}{2}$=8Hz), 2.1 (OH), 1.2 (C_{10}-CH_3) 0.75 (C_{13}—CH_3), 0.95, 0.85 (other methyl protons).

Continued elution with the same solvent system afforded 3β-chloro-5,6β-dihydroxy-5α-cholestane (LXXVI), recrystallized from light petroleum as needles, (180 mg) m.p. 125°(reported[32], m.p. 125-126°).

Reaction of 3β-hydroxy-5,6α-epoxy-5α-cholestane (L) with phenyl urea : 3β,5-dihydroxy-6β-amino-5α-cholestane (LXXVII), 3β,5-dihydroxy-6β-amino-N-formyl-5α-cholestane (LXXVIII), 3β,5-dihydroxy-6β-amino-N-phenylamido-5α-cholestane (LXXIX), 3β,5,6β-triol-5α-cholestane (LXXX)

The mixture of 3β-hydroxy-5,6α-epoxy-5α-cholestane (L) (2.5 g) and phenylurea (1.6 g) was dissolved in dimethylformamide (100 ml) and refluxed for 8 hrs. The pregress of the reaction was

monitored with t.l.c., when all of the starting material was consumed, the reaction mixture was worked up in ether and dried over anhydrous sodium sulphate. On the solvent evaporation, the residue left was column chromatographed over silica gel (75 g). Elution with light petroleum - ethylacetate (9:1) and recrystallization from light petroleum gave 3β-5α-hydroxy-6β-amino-5α-cholestane (LXXVII) (120 mg), m.p. 195°.

Analysis found : C, 76.50; H, 10.82; N, 3.03

$C_{27}H_{49}NO_2$ requires: C, 77.26; H, 11.17; N, 3.33%.

IR : ν_{max} 3480 (-OH), 3300 (-NH), 1290 and 1040 cm^{-1} (C-O).

^1H N.M.R. δ 4.85 ($W\frac{1}{2}$ = 18Hz, $C_3\alpha$-H), 4.5 (m, $-NH_2$), 3.6($C_6\alpha$-H), 6.2 (br,s, -OH, disappeared on D_2O shake), 1.09 (C_{10} $-CH_3$), 0.65(C_{13} $-CH_3$), 0.7, 0.85 (other methyl protons).

Further elution with light petroleum -ethylacetate (4:1) and crystallization from light petroleum provided 3β,5 -dihydroxy-6β-amino-N-formyl-5α-cholestane (LXXVIII) as an oil (195 mg).

Analysis found : C, 75.31; H, 10.03; N, 3.91

$C_{28}H_{49}NO_3$ requires : C, 75.11; H, 11.03; N, 3.12%.

IR : ν_{max} 3470 (-NH and -OH), 1700 and 1540 cm^{-1} ($NH-\overset{O}{\overset{\|}{C}}-H-$)

^1H N.M.R. : δ 8.1(s, -CHO), 4.9(m, -NH), 2.1(br,s, -OH, exchangeable with D_2O), 4.2 (m, $C_3\alpha$-H and $C_6\alpha$-H), 1.15(C_{10} $-CH_3$), 0.7(C_{13} $-CH_3$), 0.9 and 0.88 (other methyl protons).

Further elution with light petroleum - ethylacetate (3:1) and recrystallization from light petroleum - ethylacetate afforded 3β,5α-dihydroxy-6β-amino-N-phenylamido-5α-cholestane (LXXIX) (300 mg) m.p. 135°.

Analysis found : C, 75.32; H, 10.31; N, 5.10

$C_{34}H_{54}N_2O_3$ requires: C, 75.78; H, 10.10; N, 5.20%

IR : ν_{max} 3550 (-OH), 3350 (-NH), 1600 and 1540 (NH-C(=O)-NH-), 1650 cm^{-1} (aromatic group).

^1H N.M.R. : δ 7.33 (aromatic)), 5.3(-NH-C(=O)-NHPh), 3.5(m, $C_3\alpha$-H and $C_6\alpha$-H), 6.5 (m, -NH-C(=O)-NH-Ph), 2.2(br,s, exchangeable with D_2O), 1.15(C_{10} -CH_3), 0.7(C_{13} -CH_3) 0.9 and 0.8 (other methyl protons).

Elution with light petroleum - ethylacetate (1:1) gave 3β,5,6β triol-5α-cholestane (LXXX) (134 mg), m.p. 243° (reported[33], m.p. 240°).

Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (LI) with phenylurea : 3β-Acetoxy-5-hydroxy-6β-amino-5α-cholestane (LXXXI), 3β-acetoxy-6β-amino-N-formyl-5α-cholestane (LXXXII), 3β-acetoxy-5 hydroxy,6β-amino-N-phenylamido-5α-cholestane (LXXXIII), 3β-acetoxy-5, 6β-dihydroxy-5α-cholestane (LXXXIV)

3β-Acetoxy-5,6α-epoxy-5α-cholestane (LI) (2.5 g) and phenylurea (1.5 g) (1:5 mole) was dissolved in dimethylformamide (100 ml) and refluxed for 8 hrs. The progress

of the reaction was monitored with t.l.c., when all the starting material was consumed, the reaction mixture was worked up in ether and dried over anhydrous sodium sulphate. On the solvent evaporation, the residue was column chromatographed over silica gel (75 g). Elution with light petroleum gave 3β-acetoxy-5-hydroxy-6β-amino-5α-cholestane (LXXXI) (120 mg), m.p. 226° (reported[34], m.p. 226-228°).

Further elution with light petroleum - ethylacetate (4:1) and recrystallization from light petroleum provided 3β-acetoxy-5-hydroxy-6β-amino-N-formyl-5α-cholestane (LXXXII) (195 mg) m.p. 201° (reported[34], m.p. 200-203°).

Further elution with light petroleum - ethylacetate (3:1) and recrystallization from light petroleum afforded 3β-acetoxy-5-hydroxy-6β-amino-N-phenylamido-5α-cholestane (LXXXIII) (300 mg) m.p. 246-248°.

Analysis found : C, 74.31; H, 9.42; N, 5.01

$C_{36}H_{56}N_2O_4$ requires: C, 74.43; H, 9.71; N, 4.82%

IR : ν_{max} 3440 (-NH and -OH), 1730 (-OCOCH$_3$), 1690 and 1515 (-NH-CO-NH-Ph), 1640 cm^{-1} (NH-Ph).

Elution with light petroleum - ethylacetate (1:1) gave 3β-acetoxy-5,6β-dihydroxy-5α-cholestane (LXXXIV) (130 mg), m.p. 207° (reported[30], m.p. 209°).

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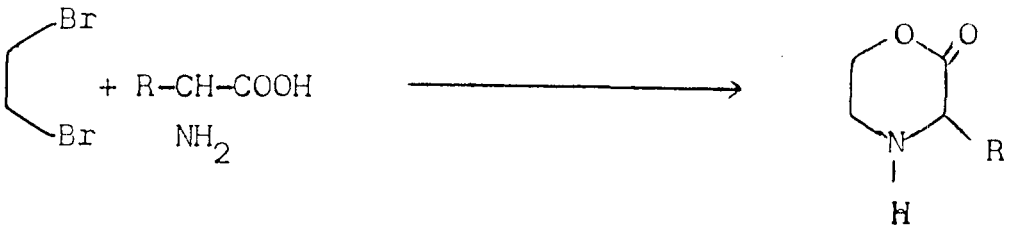

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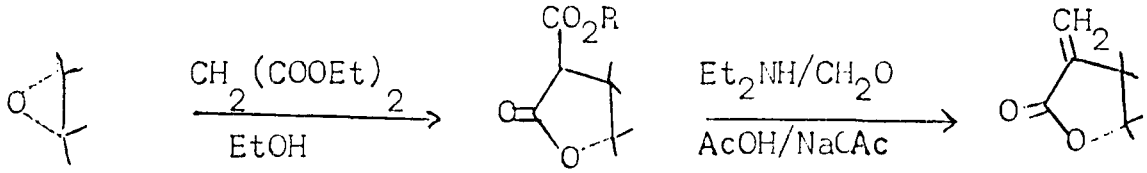

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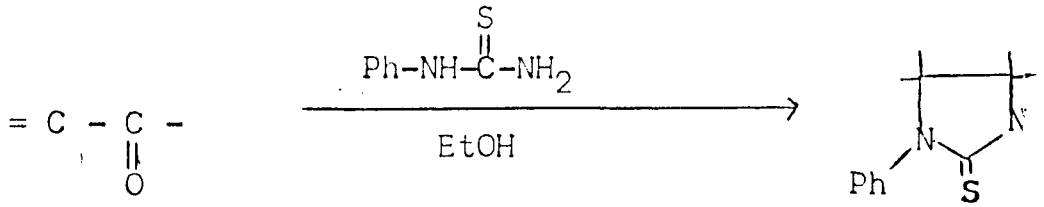

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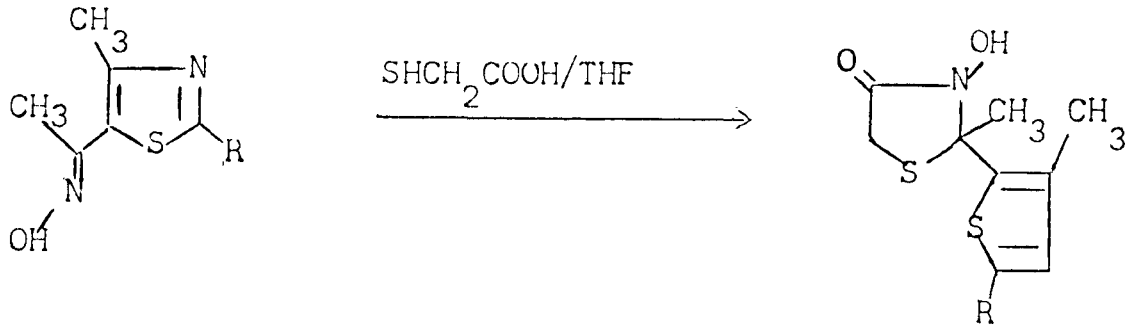
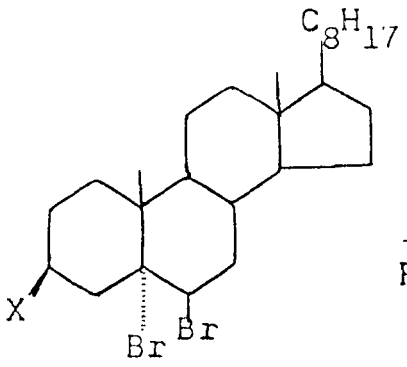


It is proposed to carry out similar reactions on the following steroidal substrates.

(1)

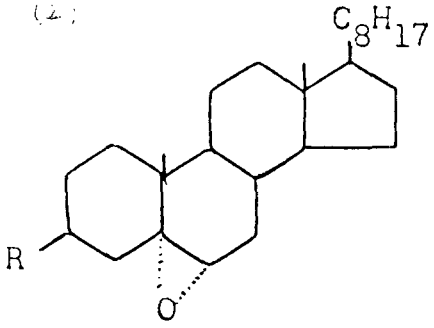


$\xrightarrow[R-CH-COOH \\ | \\ NH_2]{K_2CO_3}$ Product to be analysed.

X = Cl, OAc, H, OH

R = CH_3, C_2H_5, $=CH_2$-

(2)



$\xrightarrow[EtOH]{CH_2(COOEt)_2}$ $\xrightarrow[AcOH/NaOAc]{Et_2NH/CH_2O}$

R = Cl, OAc, H, OH

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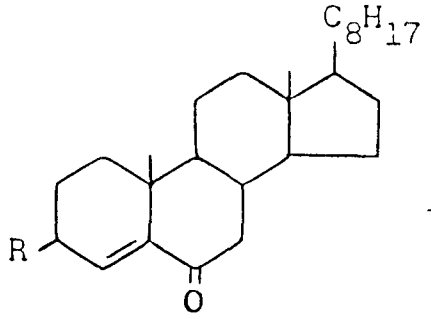

$$\xrightarrow[EtOH]{Ph-NH-\overset{\overset{S}{\|}}{C}-NH_2}$$

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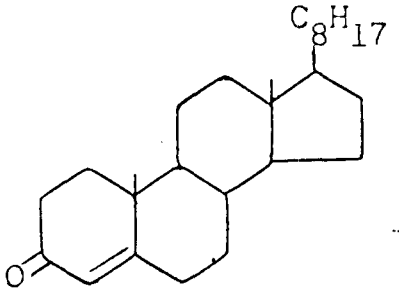
R = Cl, OAc, H, OH



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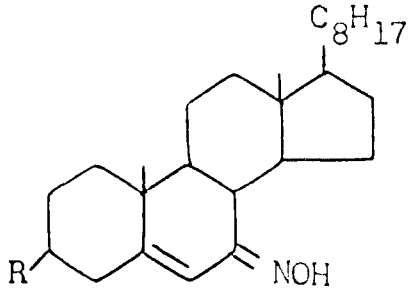
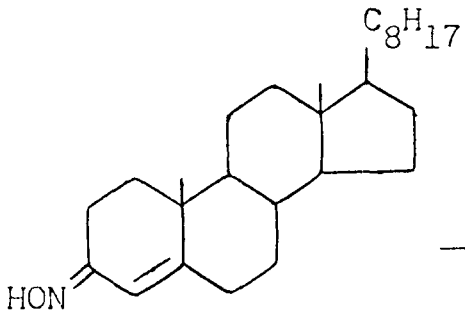


$$\xrightarrow{HS-CH_2-COOH}$$

"

R = Cl, OAc, H, OH



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